Original research article

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A COMPARISON OF ADVERSE DRUG EVENTS PROFILE OF TWO ART REGIMENS CONSISTING ZIDOVUDINE PLUS LAMIVUDINE VERSUS STAVUDINE PLUS LAMIVUDINE IN COMBINATION WITH NEVIRAPINE IN ADULT HIV/AIDS PATIENTS IN A TERTIARY CARE HOSPITAL

Rakesh K Karnani [1*], Manoj K Saurabh [2], Sapna Kamdar [3]

[1] Assistant Professor,Department of Pharmacology, Jhalawar Hospital & Medical College, Jhalawar, Rajasthan

[2] Professor and Head, Department of Pharmacology, GMERS Medical College, Gotri, Vadodara, Gujarat

[3] Assistant Professor ,Jaipur Hospital & College of Nursing, Jaipur, Rajasthan

***Email id of corresponding author-** karnanirakesh@gmail.com

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ABSTRACT:

Objective: The Antiretroviral Therapy (ART) forms the mainstay of treatment regimen against HIV/AIDS in both developed and developing countries. Unfortunately, nearly 25% of these patients discontinue their initial ART regimen because of adverse events or toxic effects of therapy. Adverse drug events caused by Anti-Retroviral Therapy (ART) varies from patient to patient and from country to country. **Material and Methods:** This prospective observational cohort study was carried out to compare the adverse drug events (ADEs) caused by fixed dose combination (FDC) containing Zidovudine-Lamivudine-Nevirapine (regimen-I) or Stavudine-Lamivudine-Nevirapine (regimen-II). The adult HIV/AIDS patients, who underwent treatment with either regimen-I or regimen-II during the study period and met inclusion criteria, were included in the study. **Result:** The total number of patients who experienced at least one ADE was '93'; out of this '59' patients were on regimen-I and '34' patients were on regimen-II. The most common ADR observed with regimen-I was anemia (40.68%) and with regimen-II was peripheral neuropathy (41.18%). **Conclusion:** Adverse drug events were more commonly reported with regimen-I as compare with regimen-II but ADEs observed with regimen-II were more severe and affect patient`s willingness to adhere with this regimen. However, there were no statistically significant difference (χ^2 value 0.3145 and p value >0.05) was seen in pattern of adverse drug events with above two regimens.

Key Words: Anti-Retroviral Therapy, Adverse Drug Events, Zidovudine-Lamivudine-Nevirapine, Stavudine-Lamivudine-Nevirapine.

INTRODUCTION

Antiretroviral therapy (ART) for the treatment of HIV infection has improved steadily since the advent of potent combination therapy in 1996. ART has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV disease into a chronic, manageable condition. Unfortunately, nearly 25% of these patients discontinue their initial ART regimen because of adverse drug events or toxic effects of therapy.(1) More than 25 antiretroviral (ARV) drugs in 6 mechanistic classes are approved by Food and Drug Administration (FDA) for

treatment of HIV infection. (2) These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs).

Government of India has started free ART centres' across the country through National AIDS Control Organization (NACO) on 1st April 2004 and as on March 2013, there are around 18.13 lakhs People Living with HIV (PLHIV) registered at the 400 ART Centers. National AIDS Control Organisation (NACO) has included '6'ARV agents in first line treatment under the National AIDS Control Programme (NACP).**(3)** The present study was carried out during the period from 1st Oct.2009 to 30th Sept.2010.
The first line ART regimens provided by NACO at that time was: **(4)**

I - Zidovudine+Lamivudine+Nevirapine (ZDV-3TC-NVP)
II - Stavudine+Lamivudine+Nevirapine (d4T-3TC-NVP)
III - Zidovudine+Lamivudine+Efavirenz (ZDV-3TC-EFV)
IV - Stavudine+Lamivudine+Efavirenz (d4T-3TC-EFV)
According to new guideline, stavudine is no longer used in first-line regimens due to its long term, irreversible and life threatening toxicities such as lipodystrophy, peripheral neuropathy and lactic acidosis. **(3,5,6)** However, In resource-limited settings stavudine continues to play a critical role in the scaling up of ART, where approximately 56% of HIV regimens still contain stavudine. **(7)** Alternative options (Zidovudine and Tenofavir) are more expensive, require more laboratory monitoring and have higher initial discontinuation rates**. (8,9)** The present prospective observational cohort study compares the adverse drug event profile of above first two ART regimens (NACO) used at ART centre, PBM Hospital Bikaner in HIV/AIDS patient.

METHODOLOGY:

This prospective observational cohort study was conducted among HIV infected patients who underwent treatment with either Zidovudine (300 mg) +Lamivudine (150 mg) + Nevirapine (200 mg) or Stavudine (30 mg)+Lamivudine (150 mg) + Nevirapine (200 mg) regimen during the period from 1st Oct.2009 to 30th Sept.2010 at ART centre of PBM and AG Hospital, Bikaner, Rajasthan (India).
Inclusion criteria were as follows: (1) HIV-infected individual's age > 18 years, (2) On treatment with either regimen-I or regimen-II for atleast 4 weeks, (3) developed at least one adverse drug event and (4) followed up at least six clinic visits in 12 months. Exclusion criteria were as follows: (1) Age <18 years, (2) seriously ill or having active major opportunistic infections (OIs), (3) pregnancy, (4) receiving medications that have drug-drug interactions with any drug of above two regimens, including rifampicin and fluconazole and (5) history of any drug abuse.
All eligible patients were followed up at monthly intervals and baseline CD4 count was estimated by CyFlow Counter (Partec). Diagnosis of various adverse events and toxicities was

performed using standard clinical and laboratory methods. Baseline laboratory investigations such as hemoglobin (Hb), total counts, differential counts, blood urea, S. creatinine, liver function tests, serum venereal disease research laboratory (VDRL) test and serum hepatitis B surface antigen (HBsAg) were carried out in patient as per requirement.

A Proforma was prepared on the basis of CDSCO-ADR reporting form **(10)** and detail history of patients who developed at least one adverse drug event (ADE) were taken and analyzed as per study objectives.

RESULTS

A total of 463 patients underwent treatment with either ZDV-3TC-NVP or d4T-3TC-NVP regimen and were followed up monthly for 12 months. Amongst '463' adult patients, '282' patients were found to receive ZDV-3TC-NVP (Regimen-I) and '181' patients were found to receive d4T-3TC-NVP (Regimen-II). A total ninety three patients have reported one or more than one adverse drug event and met entry criteria. Baseline characteristics of these 93 adult HIV/AIDS patients were shown in Table-1.

Table-1: Baseline characteristics of 93 adult HIV/AIDS patients who report Adverse drug events.

Characteristics	No. of patients (%)
Gender: Male	45 (48.39)
Female	48 (51.61)
Age group(yrs): 20-40	72(77.42)
41-60	21(22.58)
Weight: Mean (range)	50.71kg (27-72 kg)
Education : Illiterate	52 (55.91)
	21 (22.58)
Primary school	16 (17.21)
Secondary school	04 (4.3)
College & Above	
Habits : Smoking	05
Alcohol	08
Both	15
Regimen: ZDV+3TC+NVP (ZLN)	59 (63.44)
d4T+3TC+NVP (SLN)	34 (36.56)

Out of 93 patients '59' patients were receiving regimen-I and '34' patients were receiving regimen-II. The results of primary outcome and comparison of adverse drug events of both groups are shown in Table-2.

The commonest ADEs observed with regimen-I was anemia and nausea/vomiting (both 40.68% of total ADEs).

However, commonest ADE observed with regimen-II were skin reactions (rash & itching, 50%) and peripheral neuropathy (41.18%). About 2% patients have showed severe ADEs like SJ syndrome and hepatitis, which were more observed in female patients. Lipodystrophy was seen in only 1.10% of patients on regimen-II. About 75% of patients showing ADRs have CD4

count <300 cells/ml. There is statistically no significant difference in pattern of adverse drug events with two regimens (χ^2 value 0.3145 and p value >0.05). However, ADRs were more frequent with ZDV-3TC-NVP regimen (64%). The ADEs observed with d4T-3TC-NVP regimen were less in number but more severe in nature; i.e. peripheral neuropathy & lipodystrophy.

Table 2: Number of Adverse drug events caused by regimen-I and regimen-II

Adverse Drug Events	Regimen-I	Regimen-II
Anemia	24	3
Rash	11	10
Itching	4	7
Neuropathy	6	14
Nausea/Vomiting	24	6
Headache	5	3
Fatigue	2	1
SJ syndrome	4	1
Jaundice /Hepatitis	2	2
Diarrhea	3	0
Lipodystrophy	0	2

DISCUSSION

The results from the present study demonstrated that the commonest adverse drug event with regimen-I is anemia whilst with regimen-II is Peripheral neuropathy, which are similar to the findings of Kumarasamy et al **(11)** and Sharma et al. **(12)**

Anemia was seen in about 40% of the cases with regimen-I which was also comparable to 34% in an old study by Van Leeuwen et al **(13)** but less than that observed by Muneer Kanha M et al (50.8%). **(14)** The patients receiving regimen-II have reported a total of 36 (19.9%) adverse drug events during 12 months study period which was same as observed by Thai researchers. **(15)** The number of adverse drug events like nausea/vomiting and headache were also found quite similar to the study of Sharma et al. **(12)** The prevalence of lipodystrophy (1.10%) was shown to be quiet less than that reported in some western studies, this may be due to short term duration of our study**.(17,18)** In concordance with old studies hepatitis (1.1%) & S.J. Syndrome (0.5%) like severe reactions were also observed.**(15,18)** However, these reactions were found more in female patients as found by Baylor et al.**(19)**

CONCLUSION:

In the present study, there is no statistically significant difference in pattern of adverse drug events with two regimens. However, ADEs were more frequent with zidovudine-lamivudine-nevirapine regimen. The ADEs observed with stavudine-lamivudine-nevirapine regimen were less in number but has the potential to cause disfiguring, painful and life threatening side-effects, such as lipodystrophy and peripheral neuropathy. This study was carried out for short duration and long term study and surveys for adverse drug events are essential for development of treatment guidelines and improving adherence to ART regimens.

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