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ADVERSE DRUG EVENT PROFILE OF HAART REGIMEN (NACO-FDC) CONSISTING OF STAVUDINE, LAMIVUDINE AND NEVIRAPINE IN HIV/ AIDS PATIENTS.

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ABSTRACT

Adverse drug events caused by Highly Active Anti-Retroviral Therapy (HAART) varies from patient to patient and from country to country. This prospective cohort study was carried out to document the adverse drug events caused by fixed dose combination (FDC) of stavudine/lamivudine/nevirapine regimen (NACO) in HIV patients. A total of 181 adult HIV/AIDS patients received above FDC regimen during the period from October 2009 to September 2010 in ART centre of PBM and AG Hospital, Bikaner, India. Out of these '36' patients (19.9%) had shown one or more adverse drug reactions (ADRs). The mean (± SD) of age was 35.3 ± 8.13 years and of weight was 47.6± 10.8 kg. About 64% patients were found to have advanced stages of HIV infection. The patients who had shown ADRs were divided into two subgroups on the basis of CD4 cell counts (group A <200 cell/mm^3 and group B ≥ 200 cell/mm^3). The 14 patients of group A having mean (± SD) CD4 cell count 120.86±50 cells/mm^3 and 22 patients of group B having mean (± SD) CD4 cell count 409.73±176.64 cells/mm^3. The most frequently observed adverse event was skin reactions in 9.95% and peripheral neuropathy in 7.2% (out of 181) patients. Most of patients of peripheral neuropathy were from group B, i.e. 10 out of 13. However, there was no significant difference in ADR profile of group A and group B ($p>0.05$). Severe adverse events (S.J. Syndrome and hepatitis) were seen in 1.66% of total 181 patients and all were females. Lipodystrophy was observed late (after 3 yrs) in only 1.10% of patients. Nausea/vomiting and skin reactions were reported in early part of treatment. In conclusion, stavudine/ lamivudine/nevirapine regimen was safe and well tolerated by HIV-infected patients with baseline CD4 cell count<200 and ≥ 200 cells/mm^3 in resource-poor countries like India.

Keywords: *HIV/AIDS; ADRs; HAART; stavudine/lamivudine/nevirapine; resource-poor countries*.

INTRODUCTION

The Highly Active Antiretroviral Therapy (HAART) forms the bulwark of treatment regimen against HIV/AIDS in both developed and developing countries[1]. Unfortunately, nearly 25% of these patients discontinue their initial HAART regimen because of adverse events or toxic effects of therapy[2, 3]. The spectrum of adverse effects related to HAART in developing countries may not be the same as seen in developed countries due to the presence of variables like anemia, malnutrition, tuberculosis and frequent initial presentation with advanced HIV disease.

World Health Organization (WHO) guideline[4] recommends a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one NNRTI as first-line regimen in resource-poor settings based on available evidences, clinical experience and programmatic feasibility. The combination of stavudine, lamivudine and nevirapine (d4T/3TC/NVP) is the most popular combination currently in use in India[5, 6, 7].

To date, the data regarding adverse events and toxicities of the d4T/3TC/NVP regimen among HIV patients with low CD4 count are still limited in India. We therefore conducted this prospective cohort study to compare adverse drug events of d4T/3TC/NVP regimen in HIV-infected patients who had baseline CD4 cell counts <200 cells/mm^3 and those who had CD4 cell counts ≥200 cells/mm^3.

METHODOLOGY

A prospective cohort study was conducted among HIV-infected patients who were receiving FDC- d4T30/ 3TC150/NVP200 between October 2009 to September 2010 in ART centre of PBM and AG Hospital, Bikaner, Rajasthan (India). Inclusion criteria were as follows: (1) HIV-infected individual's ≥ 18 years old, (2) On treatment with d4T/3TC/NVP regimen 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

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medications that have drug-drug interactions with d4T/3TC/NVP regimen, including rifampicin and fluconazole, and (5) history of any drug abuse.

All eligible patients were divided into two groups based on their CD4 cell counts: group A (CD4 cell count < 200 cells/mm^3) and group B (CD4 cell countse" 200 cells/mm^3). 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.

A Proforma was prepared on the basis of CDSCO-ADR reporting form[8] and detail history of patients who developed at least one adverse drug event were taken and analyzed as per study objectives.

RESULTS

A total of 181 patients underwent treatment with d4T/3TC/NVP regimen and were followed up monthly for 12 months; 36 patients showed at least one adverse drug event and met entry criteria. The mean (± SD) of age was 35.3 ± 8.13 years and of weight was 47.6± 10.8 kg; 38.9% were male and 61.1% were female. About 64% of patients were found to have advanced stages of HIV infection (WHO stage III and IV). There were 14 patients (38.89%) in group A and 22 patients (61.11%) in group B; mean (± SD) CD4 count of group A and group B was 120.86±50.03 and 409.73±176.64 cells/mm^3 respectively. The results of primary outcome are shown in Table-1 and comparison of adverse events of both groups is shown in Figure-1.

Table 1: *Adverse drug events caused by stavudine/lamivudine/nevirapine. Regimen with duration of treatment*

Adverse drug events caused by d4T/3TC /NVP regimen(Total 49)	No. ofpatients reported adverse events (n=36)		Total No. of Patients (%) showing specific adverse events	Duration of treatment in months [Mean (range)]
	Group A (n= 14)	Group B (n=22)		
P. Neuropathy	3	10	13 (7.2)	22.92 (7-46)
Rashes	6	5	11 (6.08)	2.90 (1-12)
Itching	3	4	7 (3.87)	5.14 (2-20)
Nausea/Vomiting	3	3	6 (3.31)	4.67 (2-7)
Anaemia	2	1	3 (1.66)	3.5 (2-4)
SJ syndrome	0	1	1 (0.55)	1
Jaundice /Hepatitis	1	1	2 (1.10)	2
Headache	1	2	3 (1.66)	6 (2-13)
Fatigue	1	0	1 (0.55)	3
Lipodystrophy	1	1	2 (1.10)	35.5 (35-36)

The skin reactions (rashes and itching) and peripheral neuropathy were the most frequently observed adverse drug events (9.95% and 7.2% respectively) in total 181 patients. However, most of patients of peripheral neuropathy were from group B, i.e. 10 out of 13; mean duration for developing neuropathy was 22.92 months (range 7-46 months). Overall there was no significant difference in adverse drug reaction profile of group A and group B with χ^2 test ($p>0.05$).

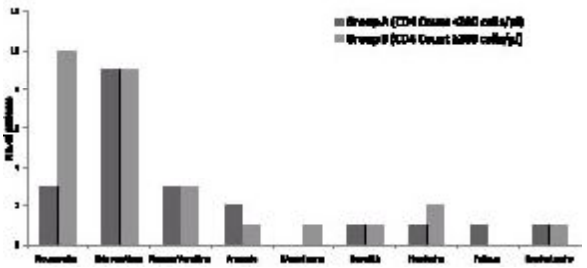

Fig. 1: *Comparison of adverse drug events caused by stavudine/lamivudine/nevirapine regimen in Group A and Group B*

Nausea/vomiting were reported by 3.31% of patient and common in early part of therapy. Skin reactions were the earliest side effects and usually appeared within 8-16 weeks of starting treatment. Severe adverse events (S.J. Syndrome and hepatitis) were seen in 3 patients (1.66%) patients and all were females. Lipodystrophy was observed in only 1.10% of patients after 3 years of treatment and only 8 patients (4.4%) stopped or changed their treatment regimen due to severe side effects and toxicities. We found that around 60-65% of adverse events could be attributed to nevirapine component of regimen.

DISCUSSION

The results from the present study demonstrate that HIV-infected patients who had baseline CD4 cell counts <200 cells/mm^3 had similar adverse drug events profile as those who had baseline CD4 cell counts e" 200 cells/mm^3. This finding can support the use of this combination of d4T/3TC/NVP in advance HIV-infected patients in the resource-limited countries like India.

A total of 36 (19.9%) patients had shown adverse events during 12 months study period which was same as observed by Thai researchers[9]. In our study, the most common adverse drug events were shown to be skin reactions (rashes and itching) and peripheral neuropathy, which resembles to the findings of Kumarasamy et al[7] and Sharma et al[10]. Nearly 6% of patients in the present study, who developed skin rashes, were also found to be similar to as observed by Sharma et al[10] but less than the study conducted in developed countries[11, 12].

The incidence of Peripheral neuropathy which was 7.2% of total patients in our study was similar to a recent (2008) south Indian study[7] but it was found more than the study conducted in Tanzania[13]. However, overall frequency of peripheral neuropathy in developed countries[14, 15] has been observed as 10-21%, which was far more than as observed in our study (7.2%). Nausea/vomiting and headache were found to be similar to the study of Sharma et al[10]. The prevalence of lipodystrophy (1.10%) was shown to be quiet less than that reported in some western studies[16, 17].

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In concordance with old studies[9, 11] hepatitis (1.1%) and S.J. Syndrome (0.5%) were also observed but these severe reactions were more common in female patients as found by Baylor et al[18]. Rashes, anaemia, hepatitis and S.J. Syndrome were observed after 4-12 weeks of treatment while lipodystrophy was seen late after 2-3 years of treatment.

In the present study, stavudine-associated lactic acidosis was not reported because of lack of laboratory test but lactic acidosis associated symptom (fatigue) was observed in one patient, this well-established adverse event should be closely monitored in the further long-term treatment. Only 8 patients (4.4%) needed to discontinue or change the regimen, so stavudine based regimen was well tolerated and until more options are accessible, it is better for scaling-up HAART in resource poor settings.

CONCLUSION

The stavudine/lamivudine/nevirapine regimen was safe and well tolerated by HIV-infected patients with baseline CD4 cell count <200 and ≥ 200 cells/mm^3. The long term and severe adverse events were observed in fewer patients as compare to western countries, so this regimen can be effectively used in advance HIV-infected patients in resource-poor countries like India. However, careful assessment of long term side effects like lipodystrophy and lactic acidosis should be made after one year treatment.

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