Original Article

Adverse effects after HAART Initiation in resource-limited settings: a prospective study from Mysore, India

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Abstract

Introduction: There are few studies from India documenting the adverse effects of generic HAART (Highly Active Anti-retroviral Therapy).
Methodology: A prospective study was conducted at Mysore, India, to study the adverse effects after HAART initiation in a cohort of 100 antiretroviral therapy (ART)-naive patients, who were evaluated prospectively every three months by clinical and laboratory monitoring for adverse effects after HAART initiation for one year.
Results: The most common first-line regimens were zidovudine (AZT) plus lamivudine (3TC) plus nevirapine (NVP) (42%); followed by Stavudine (d4T) plus 3TC plus NVP (33%); AZT plus 3TC plus efavirenz (EFV) (13%); and d4T plus 3TC plus EFV (12%).
The first-line regimen was modified in14% of patients. The most common reasons for modifying therapy were development of an adverse effect (eight cases; 57.14%) and completion of antituberculous therapy (six cases; 42.86%). The commonest cause for modifying therapy was skin rashes due to NVP (four cases) followed by anaemia two cases) and peripheral neuropathy (two cases). Grade 1 or 2 severity adverse effects by laboratory monitoring were seen in 54 patients after ART initiation and grade 3 or 4 severity adverse effects were seen in eight patients.
Conclusions: A significant proportion of patients had adverse effects of a lower grade severity after HAART. A significant proportion of those started on ART substitute therapy due to adverse effects and those on NVP-based regimens are more likely to do so when compared with those on non-NVP- based regimens.

Key words: HAART; laboratory monitoring; adverse effects

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Introduction

The World Health Organization (WHO) declared the lack of access to antiretroviral therapy (ART) a "global health emergency" in 2003, and announced an emergency plan to scale up access to ART for at least three million people by 2005 [1]. The cost of highly active antiretroviral therapy (HAART) has been brought down by various international initiatives [2]. In India, the National AIDS Control Organization (NACO) introduced inexpensive and generic ART drugs [3]. So, with the availability of generic HAART at low cost, an increasing number of HIV-infected individuals in India are now receiving therapy [4]. Many studies in developing countries have demonstrated the safety, tolerability, and efficacy of generic HAART [5,6]. However, few studies from India document the adverse effects of these drugs. This prospective study was therefore conducted at Mysore, India, to determine the adverse effects after HAART initiation in a cohort of 100 patients.

Methodology

Study design and setting

A prospective-observational cohort study involving 100 HIV-positive ART-naïve patients was conducted at the ART Centre, Krishna Rajendra Hospital, Mysore Medical College and Research Institute, Mysore, India. Duration of the study period was one year from 20 August 2006 to 19 August 2007. This study was approved by the ethics committee of our institution.

These HIV-positive individuals first underwent pre-ART counselling and were registered at the ART centre of our hospital. After clinical evaluation, informed consent was taken from these patients. They were enrolled into the study if they were found eligible for ART per the NACO guidelines and fulfilled the following inclusion criteria.

Inclusion criteria

HIV infected adults, above 18 years of age from both sexes, who satisfied the following criteria were included in the study:

1. WHO stage IV disease irrespective of CD4 cell counts, or WHO stage III disease with CD4 cell counts < 350 cells / cu. mm or WHO stage I or II disease with CD4 cell counts ≤ 200 cells/cu. mm [7].
2. Not on prior anti-retroviral therapy.
3. Having haemoglobin (Hb) value of > 10 gm/dl (for Zidovudine-based regimens). If Hb was < 10 gm/dl, patient was put on d4T (Stavudine)-based regimens.
4. ALT level no more than five times the upper limit of normal (normal levels 0-45 IU/L at 37°C), a total bilirubin concentration that did not exceed 2.5 mg/dl, a serum creatinine concentration of no more than 2 mg/dl.

Exclusion criteria

Patients who had symptoms of pancreatitis or peripheral neuropathy were excluded.

All included patients were initiated on various HAART regimens by strictly following the NACO guidelines [8]. After HAART initiation, these patients were followed up at regular intervals every three months. At each follow-up visit, complete blood count, liver function tests (serum bilirubin, AST and ALT), and serum creatinine were performed. This routine was continued up to the end of the study period. The adverse clinical events and the abnormal laboratory findings were documented.

Statistics

Descriptive statistics such as percentages and medians were calculated wherever appropriate. Comparison of NVP-based and non-NVP-based regimens was done using chi-square/Fischer's exact test and *P*-value was calculated. All *P*-values ≤ 0.05 were considered significant. All statistical analyses were performed using SPSS software (version 16.0, SPSS, Chicago, USA).

Results

The most common first-line regimens used in this cohort were zidovudine (AZT) plus lamivudine(3TC) plus nevirapine (NVP) (42%); followed by stavudine (d4T) plus lamivudine (3TC) plus nevirapine (NVP) (33%); zidovudine plus 3TC plus efavirenz (EFV) (13%); and d4T plus 3TC plus EFV (12%). Fourteen percent of patients modified their first-line regimen.

The most common reasons for modifying therapy were development of an adverse effect (eight cases; 57.14%) and completion of antituberculous therapy (six cases; 42.86%), which necessitated the change of regimen from efavirenz to nevirapine per the NACO guidelines, with median times to modify therapy being 76 days for the former and 138 days for the latter, respectively.

In those subjects with adverse effects, the commonest cause for modifying therapy was skin rashes due to NVP (four cases) followed by anaemia (two cases) and peripheral neuropathy (two cases). One patient discontinued therapy entirely primarily due to nevirapine sensitivity after a median duration of 38 days. The adverse events of various grades of severity are given in Tables 1a and 1b.

The severity of laboratory toxicities was assessed based on the WHO criteria [7]. Grade 1 or 2 severity adverse effects by laboratory monitoring were seen in 54 patients after ART initiation and grade 3 or 4 severity adverse effects were seen in 8 patients. This observation shows that the majority of patients have adverse effects after ART initiation, but of a lower grade severity.

A total of nine cases showed low haemoglobin levels during follow-up. Of these, three were of grade 4 severity (Hb < 6.5g/dL), one of grade 2 severity (7.0-7.9g/dL) and five of grade 1 severity (8.0-9.4g/dL) during the first follow-up at three months. However, these numbers dropped to six cases during the second follow-up, at which time four cases suffered adverse effects of grade 1 severity and two with adverse effects of grade 2 severity. During the third follow-up, two cases showed haemoglobin levels of grade 2 severity; however, there was no statistically significant association with zidovudine-based regimens. This result could possibly be due to the short duration of the study period as well as the improvement in the haemoglobin levels following HAART initiation.

Table 2 shows the comparison of patients who modified their first-line regimens based on whether they were on NVP-based or non-NVP-based regimens.

Table 1a. Adverse events of grade 1 or 2 severity by laboratory monitoring

Parameter	**Abnormal laboratory measurement of grade 1 or 2 severity**	**Follow-up visit**				
		Number of patients				
		I	**II**	**III**	**IV**	**Total No.**
Haematology	Hb 7-9.4 g/dL	6	6	2	-	14
	Neutrophils 750-1500 /μL	13	11	5	-	29
	Platelets 50,000-99,000 /μL	2	1	-	-	3
Renal serum chemistry	Serum creatinine 1-3 x ULN	1	-	-	-	1
Hepatic serum chemistry	AST 1.25-2.5 x ULN	-	2	-	2	4
	ALT 1.25-2.5 x ULN	-	1	-	2	3
	Serum bilirubin 1-2.5 x ULN	-	-	-	-	-
Total		22	21	7	4	54

Table 1b. Adverse events of grade 3 or 4 severity by laboratory monitoring

Parameter	**Abnormal laboratory measurement of grade 3or 4 severity**	**Follow-up visit**				
		I	**II**	**III**	**IV**	**Total No.**
Haematology	Hb< 7g/dL	3	-	-	-	3
	Neutrophils < 750 /μL	2	1	-	-	3
	Platelets < 50,000 /μL	-	2	-	-	2
Renal serum chemistry	Serum creatinine > 3 x ULN	-	-	-	-	-
Hepatic serum chemistry	AST > 5 ULN	-	-	-	-	-
	ALT > 5 ULN	-	-	-	-	-
	Serum bilirubin 2.5 - >5 x ULN	-	-	-	-	-
Total		5	3	-	-	8

Note: These parameters are strictly per the WHO guidelines [8].

Table 2. NVP-based regimens versus non-NVP-based regimens: comparison of patients who modified first-line regimen from Mysore (2006-2007) (N = 100)

Content	**NVP-based**	**Non-NVP-based**	**total**	**p**
Total number on first-line regimen	73(73%)	27(27%)	100	
Number who modified first-line regimen	7(7%)	7(7%)	14(14%)	0.05,N.S.
Median time on therapy for those who modified first-line regimen	77(22.1-120.78)	118(76.67-187)	86.5(65.40-137.88)	0.10
Reasons for modifying first-line regimen				
Adverse Effects	7	1	8	0.0047
Completion of ATT	0	6	6	0.0047

Discussion

In the present study, the first-line regimens used in the majority of the cases (75%) were nevirapine-based, as they are inexpensive and are available free of cost through NACO.

More patients on NVP-containing regimens were likely to substitute therapy due to adverse effects than those on non-NVP containing regimens (P= 0.0047). Discontinuation of therapy due to lack of financial resources was one of the important factors previously reported by Kumaraswamy *et al*. [4]. However, in the present study, affordability was not at all a factor, as all the drugs were given free of cost by NACO. This aspect shows that the discontinuation of therapy on account of cost can be offset by the WHO public health approach of providing ART drugs at no (or a very subsidized) cost.

Most of the patients with active tuberculosis were started on efavirenz-based regimens. On completion of anti-tuberculous therapy (ATT), the regimen was modified to stavudine/zidovudine-based regimens, per the NACO guidelines (six cases). This modification was primarily due to the increased cost of the efavirenz-based regimens.

In conclusion, a significant number of patients on ART developed grade 1 or grade 2 severity adverse effects, which could be detected only by laboratory monitoring and thus underlines the importance of regular follow-up of these patients. A significant proportion of those started on ART substituted therapy due to adverse effects. Those on nevirapine-containing regimens were more likely to do so in comparison to those on non-nevirapine based regimens. Providing ART drugs at low or no cost improves outcomes by discouraging discontinuation of therapy on account of non-affordability, which is a constant problem in resource-limited settings.

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