Evaluation of adverse drug reactions in HIV positive patients in a tertiary care hospital

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Abstract

Context: The advancement and development of new drugs and treatment strategies increase the risk of unusual Adverse Events (AEs) in HIV patients. Aims: The objective of our study was to assess the incidence, types and nature of AEs in HIV positive subjects. Settings and Design: Patients with WHO stage IV disease irrespective of the CD4 cell count, or WHO stage III disease with a CD4 cell count <350 cell/cu. mm, or, WHO stage I or II disease with a CD4 cell count of <200 cells/cu. mm, and on prior anti-retroviral therapy for not more than six months preceding the observation date, were included in the study. After initiation of therapy, the patients were examined for the occurrence any adverse events including the type and severity, or any other abnormal laboratory findings. Causality assessment of the adverse events was done using the Naranjo’s scale. Results: Out of 327 patients studied prospectively, 43 patients developed AEs. Out of these, 23 (53.5%) were males and 20 (46.5%) were females. A total of 53 (16.21%) AEs were reported. Antitubercular drugs caused the maximum AEs (28.3%) followed by zidovudine (20.7%), nevirapine (15.0%) and efavirenz (5.6%). Stavudine, ethambutol, sulfamethoxazole and trimethoprim, and atazanavir were also responsible for 3.7% of AEs individually. Causality assessment done according to the Naranjo’s scale revealed that 66.04% AEs were ‘probable’ and 33.96% were ‘possible’. Conclusions: Anemia, hepatitis and dermatological adverse effects are the most common AEs. Antitubercular drugs contributed significantly for the incidence of AEs in these patients. Frequency of AEs was slightly more in males compared to females.

Key Words: Adverse events, anti-retroviral therapy, HIV

INTRODUCTION

Pharmaco-vigilance has been defined as the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible medicine related problem.[1] Adverse Events reporting directly adds to the increased vigilance and may even influence the recommendation of drugs used through the regulatory authorities.[2] The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS-related morbidity and mortality.[3] In India, NACO has made efforts to make generic HAART available, which is very economical, due to which many HIV infected individuals are receiving the therapy.[4] Many studies in developing countries have
demonstrated the safety, tolerability and efficacy of generic HAART.[8] The major toxicities include bone marrow suppression, pancreatitis, hypersensitivity, hepatic necrosis, neuropsychiatric complaints, and nephrolithiasis.[6,4] The objective of our study was to assess the incidence, types and nature of AEs in HIV positive patients.

**MATERIALS AND METHODS**

A prospective-observational study was conducted at the Anti-retroviral therapy (ART) center of a tertiary care hospital in Mangalore. The study was conducted over a period of two months involving all the HIV-positive subjects registered within this time period. Due permission was obtained from the Nodal Officer of the centre. The study was undertaken after obtaining approval from the institutional ethics committee.

Patients with WHO stage IV disease irrespective of the CD4 cell count, or WHO stage III disease with CD4 cell count <350 cell/cu. mm or WHO stage I or II disease with a CD4 cell count of <200 cell/cu. mm[7] and on prior anti-retroviral therapy for not more than six months preceding the observation date were included in the study. Patients with pancreatitis or peripheral neuropathy and who were on ART for a duration of more than six months were excluded from the study. The subjects were selected by purposive sampling method. All selected subjects were initiated on a HAART regimen that strictly followed the guidelines laid down by NACO.[8] After initiation of the therapy, the patients were examined for any adverse event that occurred, its type and severity, or any other abnormal laboratory finding. These subjects were followed up for a period of two months. At each follow-up visit, the adverse clinical events and the abnormal laboratory findings were documented.

The case sheets of the included subjects were studied and the information obtained was entered into the Suspected Adverse Event Reporting Form. All the information collected was kept confidential and the identity of the subject was not disclosed. The subjects were not interviewed by the investigator. Information on all the subjects including demographic details, relevant history, examination details, investigations and drug therapy were detected and recorded in the adverse drug reaction reporting form. When any other information was required, the treating physician was contacted. Any AE observed by the investigator or treating physician was noted in the form and any untoward event was labeled as an AE only after the concurrence of treating physician. In case of any difference of opinion with respect to reaction, treating physician’s opinion was considered as final. To confirm adverse events, some investigations were required; they were carried out with the consent of the concerned physician. In this study only AE was monitored. No observations were made in the diagnosis or management of the subject. The details of ART as well as other concomitant medication with the date of starting the medication, duration of therapy, dosing regimen, route etc., were noted. Details of AE collected included type, severity, seriousness, outcome, treatment given and causality assessment as per Naranjo’s scale[9] (Scoring: ≥9 = definite AE, 5-8 = probable AE, 1-4 = possible AE, 0 = doubtful).

**Statistical analysis**

Descriptive statistics such as percentages were calculated wherever appropriate. Data was sub-divided based on age, sex, drugs and body systems/organ involved. Incidence of AE, time of occurrence of AE and total number of drugs administered were calculated.

**RESULTS**

Out of 327 patients studied prospectively, 43 patients developed AEs, of which 23 (53.5%) were males and 20 (46.5%) were females. A total of 53 (16.21%) AEs were reported. The incidence, causality, type of AE, and the system/organ involved were shown in Table 1. The most common AE was dermatological, followed by hepatic, hematological, general (weight loss and fever), nervous system, metabolic, ear, heart, muscle, gastrointestinal tract.

On further analysis of these 53 AEs incriminated by individual drugs in 43 patients it was found that

**Table 1: Comparison of adverse events to anti retroviral therapy among males and females**

| Characteristics       | Male (%) | Female (%) | Total (%) |
|-----------------------|----------|------------|-----------|
| Incidence             | 23 (53.5)| 20 (46.5)  | 43 (100)  |
| Causality assessment  |          |            |           |
| Probable              | 18 (51.4)| 17 (48.6)  | 35        |
| Possible              | 08 (44.4)| 10 (55.6)  | 18        |
| System/Organ involved |          |            |           |
| Blood general         | 5 (35.7) | 9 (64.2)   | 14        |
| Weight loss           | 8 (66.6) | 4 (33.3)   | 12        |
| Fever                 | 5 (62.5) | 3 (38.5)   | 08        |
| Nervous system        |          |            |           |
| Metabolic             | 0 (00.0) | 1 (100)    | 0         |
| Ear                   | 4 (80.0) | 1 (20.0)   | 06        |
| Heart                 | 1 (20.0) | 4 (80.0)   | 05        |
| Muscle                | 1 (25.0) | 3 (75.0)   | 04        |
| GIT                   | 1 (100)  | 0 (00.0)   | 01        |
| GIT                   | 1 (100)  | 0 (00.0)   | 01        |
| GIT                   | 0 (00.0) | 1 (100)    | 01        |
| Total                 | 26 (49.0)| 27 (51.0)  | 53        |
ATT caused the maximum AEs (28.3%) followed by zidovudine (20.7%), nevirapine (15.0%), efavirenz (5.6%). Each of stavudine, ethambutol, sulfamethoxazole and trimethoprim, and atazanavir were responsible for 3.7% of AEs individually. Also, each of amoxicillin, nimesulide, rifampicin, streptomycin, and acyclovir were responsible for 1.8% of the total AEs [Table 2]. Among the total adverse events 47.1% were due to ART and the remaining 52.9% were due to other drugs.

Out of the 53 AEs, three were fatal, and two were life threatening. Of the three that were fatal, two were associated with lactic acidosis. One was induced by zidovudine, due to which the patient died of shock and the other one was due to ATT-induced hepatitis which further led to hepatic encephalopathy, causing the death of the patient. Among the two life threatening AEs, one was Stevens-Johnson syndrome associated with nevirapine and the other one was atrial fibrillation which was induced by acyclovir.

**Table 2: Adverse drug reactions in HIV patients**

| Drugs | AEs (no. of patients) | No. of patients (%) |
|-------|-----------------------|---------------------|
| Anti-Tubercular Drugs (either H/R/Z/E) | | |
| | | |
| Zidovudine | Anemia-8 | 11 (20.7) |
| | Lactic acidosis-2 | 2 (3.7) |
| | Proximal myopathy-1 | 1 (1.8) |
| Nevirapine | Rash-5 | 8 (15.0) |
| | Stevens-Johnson syndrome-1 | 1 (1.8) |
| | Fever-1 | 1 (1.8) |
| Efavirenz | Giddiness-2 | 3 (5.6) |
| | Weight loss-1 | 1 (1.8) |
| Stavudine | Lactic acidosis-2 | 2 (3.7) |
| Ethambutol | Optic neuritis-2 | 2 (3.7) |
| Sulfamethoxazole and trimethoprim (Bactrim) | Rash-1 | 2 (3.7) |
| | Rash with erythema over lips-1 | 1 (1.8) |
| Sulfamethoxazole and trimethoprim (Sepran) | Rash-1 | 2 (3.7) |
| | Rash leading to exfoliative dermatitis-1 | 1 (1.8) |
| Atazanavir | Jaundice-2 | 2 (3.7) |
| | Fever-1 | 1 (1.8) |
| Anti-Retroviral Therapy (eitherZT/3TC/EFV) | Rash-1 | 1 (1.8) |
| Amoxicillin | Urticaria-1 | 1 (1.8) |
| Nimesulide | Rash-1 | 1 (1.8) |
| Rifampicin | Hepatitis-1 | 1 (1.8) |
| Streptomycin | Otoxicity-1 | 1 (1.8) |
| Acyclovir | Atrial Fibrillation-1 | 1 (1.8) |
| Total | | 53 (100) |

**DISCUSSION**

Occurrences of adverse events are one of the commonest causes for poor adherence to treatment. Hence, evaluation of AEs may help clinicians to optimize the drug regimens. The present study has reported the incidence, type, causality and has also attempted to profile the suspected AEs occurring in HIV positive patients in an ART center attached to a tertiary care teaching hospital over a period of two months.

The present study has shown the frequency of AEs in HIV patients as 16.21%. This was comparable with the prevalence of 17.5% reported by Modayil et al. The prevalence of AEs in a study done by Srikant et al. was higher in female population (41.82% [31/78]) compared to males (33.05% [40/121]). In contrast to this, our study has shown a higher prevalence in males compared to females (53.5% males and 46.5% females). In a study done by Nagpal et al. 90.6% patients receiving ART experienced AEs. They reported a total of 618 AEs involving various systems. Majority were related to gastrointestinal (42.39%) and central nervous (25.57%) system. This was substantially higher than the prevalence of 17.5% reported by Modayil et al.

Our study has shown that the most common AE was associated with antitubercular drugs accounting for 28.3% of the total AEs. Hepatitis was the most common AE attributed to anti-tubercular drugs. Out of the seven cases of hepatitis reported, one progressed into hepatic encephalopathy leading to death. The anti-tubercular drugs were also associated with AEs such as fever, rash, nausea and vomiting. As documented in the literature, ethambutol has caused optic neuritis in two patients in the study. Hepatitis due to rifampicin alone was documented to be 1.8% as compared to 1.1% in a study conducted by Khan et al. Liver function was improved after rifampicin was stopped. Streptomycin induced ototoxicity contributed to 1.8% of the total AEs. Studies done by Waguespack et al. and Kenyon et al. have well established the relationship between streptomycin and ototoxicity and the mechanism that causes it.

The second most common AE encountered in this study was due to zidovudine accounting for 15% AEs. In a study conducted by Curkendall et al. the incidence of zidovudine induced anemia was 24.3%. Zidovudine causes bone marrow suppression leading to anemia and thrombocytopenia. Agarwal et al., reported high incidence of zidovudine-induced anemia in HIV-infected patients in eastern India.

Lactic acidosis and proximal myopathy were also reported in our study. Two of the patients died due to...
lactic acidosis. Lactic acidosis is one of the most serious presentations of nucleoside analogue reverse transcriptase inhibitor (NRTI) associated mitochondrial toxicity. Although this complication is rare, the associated mortality rate may be high. Lactic acidosis is one of the established adverse effects of stavudine.\(^{[18,19]}\) According to a study conducted by Agu et al. Stavudine based regimens have lesser AE as compared to Zidovudine based regimen, commonest being peripheral neuropathy and skin rash.\(^{[20]}\)

Around 15% of AEs were due to nevirapine. Among these, the most common AE was rash, accounting for 9.4% of the cases. One case of Stevens-Johnson syndrome was also reported with nevirapine and the patient succumbed to death. Fagot et al.\(^{[21]}\) also reported the association of nevirapine with Stevens-Johnson syndrome. This drug also caused fever and hepatitis which constituted 1.8% each. Chen et al., have induced skin rash by the use of nevirapine in rats and determined that the 12-hydroxylation metabolic pathway is responsible for the rashes.\(^{[22]}\)

Cotrimoxazole induced rash was found to contribute to 3.7% of the total AEs. Skin rashes including the fatal Stevens-Johnson syndrome were the well documented adverse effects of sulfonamides.\(^{[23,24]}\) One patient in this study, who was on cotrimoxazole, progressed to exfoliative dermatitis.

Amoxicillin induced rash was reported in one of our patient, thus constituting 1.8% of the total AEs reported in the study. The rash disappeared after the drug was stopped. This finding was supported by a Spanish study conducted by Santiago Sánchez-Mateos et al.\(^{[25]}\) Nimesulide, a selective COX-2 inhibitor, also led to rash in one of our patients. Nimesulide induced rash was described in an earlier study also.\(^{[26]}\)

Dermatological toxicities are common complication of HIV infection and this is a significant risk factor for adverse events. In HIV-infected patients, there is a high prevalence of hypersensitivity reactions induced by antiretroviral therapy. Furthermore, HIV-infected patients may have recurrent cutaneous reactions from other medications such as antibiotics, non-steroidal anti-inflammatory drugs and anti-tuberculosis agents. Withdrawal of the suspected drug is essential for prognosis. The rapid detection and treatment of cutaneous adverse events, plus identification of the causative agent, are essential for preventing the progression of the reaction, preventing additional exposures and ensuring the appropriate use of medications for the current condition and for other conditions.

Giddiness can be attributed to efavirenz as it is known to be associated with CNS adverse effects.\(^{[27]}\) Weight loss could be due to efavirenz. It can be also explained by the primary disease or concomitant opportunistic infections.

Two patients taking atazanavir, a protease inhibitor, showed the AE of jaundice constituting 3.7% of the total AEs and the drug was withdrawn. A Spanish study done by Palacios et al.\(^{[28]}\) showed a relation between the use of atazanavir and jaundice.

One of the rare AE, atrial fibrillation induced by acyclovir was noted in one out of 53 AE i.e. 1.8%. FDA reports for this drug, shown atrial fibrillation as one of its AE, being reported in 1.51%-2.02% of patients.\(^{[29,30]}\)

Causality assessments, according to Naranjo’s scale, revealed 66.04% AEs were ‘probable’ and 33.96% were ‘possible’. It is important to perform a causality assessment according to WHO causality assessment scale or Naranjo’s scale of the suspected drug reaction in order to determine whether drug discontinuation is mandatory, as well as to put emphasis on patient education in order to avoid the development of AEs in the future.

Limitations of our study should also be considered. The follow-up period is too short and the study is limited to one ART center. Multicentric studies involving large sample size are required to provide more valuable data on incidence and pattern of AEs in HIV patients.

To conclude, anaemia, hepatitis and dermatological adverse effects are the most common AEs. Antitubercular drugs contributed significantly for the incidence of AEs in these patients. Frequency of AEs was slightly more in males compared to females. Healthcare professionals who attend to HIV-infected patients must have a profound knowledge of the safety profile of the drugs and also need to report any AE that may occur when the patients are on these drugs.

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