Adverse drug reaction monitoring in patients on antiretroviral therapy in a tertiary care hospital in Eastern India

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Abstract:
BACKGROUND: Besides unparalleled benefits, highly active antiretroviral therapy is also associated with wide range of potential adverse drug reactions (ADRs), which hinders treatment adherence. The present study was thus designed to monitor and explore the pattern of occurrence of ADRs to various antiretroviral therapy (ART) regimens in a tertiary care ART setup.

MATERIALS AND METHODS: A prospective, observational clinical study was carried out in the outpatient setting of nodal ART center of Eastern India. A total of 610 patients on various ART regimens were studied for suspected ADRs over 12 months. Adverse event history, medication history, and other relevant details were captured. Causality and severity of each reported ADR were duly assessed.

RESULTS: 32.45% patients of total study participants presented with a total of 330 ADRs. Patients from zidovudine-based regimens presented with majority of ADRs such as anemia (up to 36%), central nervous system (CNS), and gastrointestinal (GI) side effects. Tenofovir-based regimens were, however, found to be mildly safer. The combination with Efavirenz was associated with majorly CNS side effects while that of nevirapine was associated with rash and pigmentation of nails. Atazanavir boosted second-line regimens were notably associated with increased serum lipid levels followed by other GI and CNS adverse effects. Increased liver enzymes were found in atazanavir-based second-line ART.

CONCLUSION: The study enables to obtain information on the incidence and pattern of ADRs associated with various antiretroviral regimens, thereby reducing its occurrence and protecting the patient population from avoidable harm. Need of intensive monitoring for ADRs in ARTs thus seems to be a mandate.

Keywords: Adverse drug reactions, antiretroviral therapy regimens, human immunodeficiency virus

Introduction

The human immunodeficiency virus (HIV) disease continues to be a serious global health issue. Recent statistics states that there were about 2 million new cases of HIV in 2014. Of about 36.9 million people living with HIV (PLHIV) around the world, around 15.8 million people have been receiving antiretroviral therapy (ART).[1] The introduction of this therapy in the developed countries in the late 90s and the subsequent progress in providing its accessibility globally has been associated with a remarkable decrease in AIDS-related mortality, which has changed the outlook of HIV infection from being a rapidly fatal to a chronically manageable infection.[2] Antiretrovirals mainly suppress viral load, thus restoring the immune function. Declining costs of antiretrovirals along with the production of drugs by generic manufacturers has helped tertiary care centers in resource-limited areas cater better antiretroviral care to HIV-seropositive population.[3] Despite

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showing considerable efficacy in reducing mortality and morbidity in PLHIV, ART is also associated with wide range of potential adverse effects leading to reduction in patient’s quality of life and adversely affecting treatment adherence which may consequently lead to treatment failure. Adverse drug reactions (ADRs) to these medications remain a significant point of concern which may subsequently compromise the effectiveness of an ART program. ADRs due to continuous exposure to antiretroviral drugs leaves the caregiver with limited options such as decreasing the dosage of antiretroviral drugs, withdrawing the offending drug or substituting it with another drug or symptomatically treating the ADR(s). However, substituting the offending drug is cumbersome, especially in resource-limited settings as most highly active antiretroviral therapy (HAART) regimens come as fixed dose combinations of different drugs having varied toxicity profiles.\[4\]

ADRs account for considerable mortality and morbidity besides having immense economic impact on patients, health-care providers and society. Most of the ADRs are preventable. The incidence of ADRs among patients on antiretrovirals from both developing and developed countries ranges between 11% and 35.9%\[5,6\] with incidence being as high as 54%\[7,8\] coexistent with opportunistic infection. The long-term effects of antiretroviral medications are largely unknown though various ongoing researches are providing deeper insights into some adverse reactions of these drugs. The present study was thus designed to monitor and analyze the pattern of occurrence of ADRs to ART regimens in a tertiary care ART setup.

Materials and Methods

A prospective, longitudinal, observational clinical study was carried out for a period of 1 year (September 2014–August 2015) in PLHIV-receiving ART in the outpatient setting of a nodal ART center of Eastern India. Institutional ethics committee approval was taken the initiation of the study and written informed consent was obtained from all subjects before their inclusion in the study. Confidentiality of information was duly maintained and basic principles of ethics in clinical research were strictly followed. All consecutive treatment naïve subjects of either sex aged 18 years or above, put on ART were included in this study. Subjects having treatment modifications due to virological or immunologic failure, pregnant women, lactating mothers, patients having any other comorbidities such as psychiatric illness, diabetic mellitus, hypertension, chronic kidney disease, etc., were excluded from the study. Data regarding patient demographics and clinical information were collected in a prestructured pro forma. ADR diagnosis was based on patient complaints and physician diagnosed changes (if any) during routine clinical examination. ADRs reported were subsequently followed up. Adverse event history, medication history, and other relevant details were captured in a format as adopted in the Pharmacovigilance Programme of India (PvPI). Causality of ADR was assessed using Naranjo’s ADR probability scale and WHO-UMC causality scale, respectively. The severity of each reported ADR was assessed using Hartwig and Siegel Scale. Descriptive statistical analysis of the obtained data was performed.

Results

A total of 610 patients were screened for the study, of which males represented 56.06% (n = 342) of the population. Out of the total population, 108 males (31.58%) and 90 females (33.58%) presented with one or more ADRs. Thus, a total of 198 patients (32.45%) reported with 330 ADRs. As some patients had more than one ADR during the same visit, the total number of ADRs was greater than the total number of patients experiencing a reaction. In cases where an identical reaction occurred more than once in the same patient during the visit, the patient was documented as having experienced a single reaction. Age group analysis revealed that patients within the age group of 51–60 years presented with maximum ADRs, followed by 41–50 years and 18–30 years, respectively [Table 1].

Out of the various three drug ART regimens prescribed under NACO program, zidovudine-based first-line recipients (40%) presented with maximum ADRs (ZLN [39.30%]; ZLE [43.64%]). Among the second-line regimens, zidovudine and boosted atazanavir combination recipients (57.14%) presented with maximum ADRs [Table 2].

Out of 330 ADRs reported, zidovudine-nevirapine based first-line regimens (36.06%) accounted for maximum reported ADRs followed by zidovudine-efavirenz (EFV)-based regimens (25.45%).

Assessment of the total ADR profile revealed, nervous system disorders accounting for the maximum

| Table 1: Patients presenting with adverse drug reactions |
|-----------------------------------------------|
| **Total patients screened** | **Total patients presenting with ADRs** |
| 18-30 years | 152 | 49 |
| 31-40 years | 305 | 97 |
| 41-50 years | 109 | 36 |
| 51-60 years | 36 | 14 |
| ≥61 years | 8 | 2 |
| Total | 610 | 198 |

ADRs=Adverse drug reactions
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ADRs (26.36%), followed by gastrointestinal (GI) (23.33%), and metabolism disorders (20.91%) [Figure 1].

Among various GI disorders, majority presented with complaints of nausea and increased liver enzymes. Insomnia and headache were mostly reported ADRs from nervous system class. Various skin disorders reported as ADRs included rashes and nail pigmentation. Severe ADR requiring hospital admission includes four cases of Stevens-Johnson syndrome (two cases each from TLE and TLN regimen, respectively). Increased lipid level was the most commonly reported ADR (20.91%), followed by anemia (17.57%) [Table 3].

Patients from zidovudine-based regimens such as ZLN and ZLE presented with the majority of ADRs such as anemia (up to 36%), central nervous system (CNS) side effects (up to 33%), and GI side effects (up to 24%). Tenofovir-based regimens were, however, found to be mildly safer. Combination with EFV was associated with majorly CNS side effects while that of nevirapine was associated with rash and pigmentation of nails (up to 55%). Lopinavir boosted second-line regimens were notably associated with increased serum lipid levels followed by other GI and CNS adverse effects. Increased liver enzymes were found in atazanavir-based second-line ART [Table 4].

Out of 330, ADRs assessed for causality using Naranjo’s algorithm[8] and WHO-UMC causality assessment scale,[9] 289 ADR cases (87.57%) were found to be “probable” while 41 (12.42%) were found to be “possible.” WHO-UMC causality assessment scale showed 83.03% (n = 274) as “probable/likely” and 16.97% (n = 56) as “possible.”

Severity was assessed using Hartwig and Siegels Scale,[10] 83.33% of the cases were found to be mild while 16.06% and 0.6% of the cases were found moderate and severe, respectively [Figure 2].

Discussion

With the advent of HAART, millions of eligible HIV-infected patients are now having better access to antiretroviral drugs; subsequently leading to considerable decrement in HIV-related morbidity and mortality globally. However, the adverse effects of these drugs is a matter of increasing concern in the treatment of PLHIV owing to the need of maintaining ART indefinitely to achieve clinical benefits. Adverse reaction to antiretrovirals in PLHIV is a major cause of nonadherence to therapy, leading to subsequent treatment failure.[11-13] The present study thus monitored the ADR pattern in patients receiving antiretroviral therapy in a nodal ART care centre.

Our study revealed that out of the various three drug antiretroviral regimens prescribed under NACO programme, zidovudine-based first-line recipients presented with maximum ADRs. Among the second-line regimens, zidovudine and boosted atazanavir combination recipients presented with maximum ADRs. Zidovudine-nevirapine based first-line regimens accounted for maximum reported ADRs followed by zidovudine-EFV based regimens.

Our study revealed that nervous system disorders accounted for the maximum number of reported ADRs, followed by GI, and metabolism disorders. Combination with EFV was majorly associated with CNS side effects,
such as insomnia, headache, numbness, dizziness, etc., For most patients, these side-effects resolved within 6–10 weeks of starting treatment, but for some patients, symptoms seemed to wax and wane long term. CNS side effects generally become more tolerable and resolve within the first 4 weeks of therapy. EFV-associated adverse events may compromise adherence to treatment and lead to treatment discontinuation. Some studies have reported treatment discontinuation rates ranging from 4% to 46% related to neuropsychiatric side effects of EFV.\cite{14,15} Clinicians should counsel patients having possible CNS effects of EFV and look for behavioral and cognitive changes. In case of persistent or intolerable side effects, a switch in HAART regimen may be found appropriate. Despite being a part of first-line treatment, many patients receive EFV only after experiencing treatment failure on earlier HAART regimens. Therefore, patients who switch to EFV and then experience neurologic or psychiatric side-effects are left with limited options for future antiretroviral treatment. Careful considerations regarding risks and treatment alternatives for these patients are required.\cite{16}

Among various GI disorders, majority presented with complaints of nausea and increased liver enzymes. Liver enzymes elevations of varying degree have been reported with all classes of approved antiretroviral drugs. Severe cases of hepatotoxicity with fatal outcomes have been reported with ARV therapy, and increased liver enzymes have been a common clinical reason for this therapy discontinuation in clinical practice. The mechanisms though unclear majorly hint at mitochondrial toxicity resulting from nucleoside reverse transcriptase inhibitors (NRTIs) use and hypersensitivity reactions to nonnucleoside reverse transcriptase inhibitors (NNRTIs).\cite{17} The present study reports increased liver enzymes in boosted atazanavir regimens accounting for 4.54% of total ADRs. In our set up, skin and subcutaneous tissue disorders accounted for 7.88% of the total ADRs. Various skin disorders reported as ADRs included rashes and nail pigmentation, which were majorly reported from nevirapine-based regimens, which are presumably immune mediated responses. Steven–Johnson syndrome was observed in four patients, three of them were in nevirapine-based regimens while one was in EFV-based regimen. Dechallenging and subsequent regimen switch over to EFV and nevirapine-based regimens, respectively, were found successful. No rechallenge was however attempted.

### Table 3: Frequency of various adverse drug reactions

| ADR description                                      | Frequency (%) |
|------------------------------------------------------|---------------|
| Gastrointestinal disorders                           |               |
| Anorexia                                             | 8 (2.42)      |
| Nausea                                               | 24 (7.27)     |
| Vomiting                                             | 12 (3.64)     |
| Abdominal pain                                       | 13 (3.94)     |
| Abdominal cramps                                     | 1 (0.3)       |
| Diarrhea                                             | 2 (0.61)      |
| Gastric intolerance                                  | 2 (0.61)      |
| Increased liver enzyme levels                        | 15 (4.54)     |
| Nervous system disorders                             |               |
| Insomnia                                             | 34 (10.30)    |
| Giddiness                                            | 1 (0.3)       |
| Headache                                             | 26 (7.88)     |
| Peripheral neuropathy                                | 2 (0.61)      |
| Numbness                                             | 8 (2.42)      |
| Tremors                                              | 3 (0.91)      |
| Dizziness                                            | 8 (2.42)      |
| Nightmares                                           | 5 (1.51)      |
| Skin and subcutaneous tissue disorders               |               |
| Rashes                                               | 17 (5.15)     |
| SJS                                                   | 4 (1.21)      |
| Pigmentation of nails                                | 5 (1.51)      |
| Musculoskeletal and connective tissue disorders      |               |
| Generalized weakness                                 | 2 (0.61)      |
| Body ache                                            | 8 (2.42)      |
| Muscle cramps                                        | 2 (0.61)      |
| Blood and lymphatic system disorders                 |               |
| Anemia                                               | 58 (17.57)    |
| Pallor                                               | 1 (0.3)       |
| Metabolism and nutrition disorders                   |               |
| Increased lipid levels                               | 69 (20.91)    |

ADR=Adverse drug reactions, SJS=Stevens-Johnson syndrome
The present study showed that lipid abnormalities remained the maximum reported ADR. It accounted for 20.91% of the total ADRs. In vitro studies have suggested that protease inhibitors (PIs) may influence lipid metabolism by interfering with the degradation by proteasomes in hepatocytes and adipocytes, thereby influencing gene expression involved in lipid metabolism. Specific PIs differ in their lipid effects in vitro. Increased lipid levels were found in boosted PI based second-line ART regimens especially. PI-associated insulin resistance and altered expression of the apolipoprotein C-III gene may also mediate PI-associated dyslipidemia. Atazanavir boosted second-line regimens were notably associated with increased serum lipid levels. Other studies have also conferred similar results.

Anemia accounted for a total of 17.57% of total ADRs in our study, which was majorly reported from patients on zidovudine-based regimens such as ZLN and ZLE. Zidovudine is documented to cause anemia by bone marrow suppression and inhibition of proliferation of blood cell progenitor cells in a time- and dose-dependent fashion. Tenovifor-based regimens were however found to be milder in this regard.

Our study had certain limitations. Being an OPD-based study, it is quite possible that some ADRs were missed that were transient or too mild to have inconvenienced the patient to report. Moreover, the study was conducted for a short period at a single center with a small sample size monitoring a fraction of Eastern India population, thus the data cannot be a representative of national statistics. The study failed to identify the potential predictors of ADRs to ART in HIV-infected patients. The study may not be a representative to true ADR detection rates as data are largely generated by spontaneous reporting.
system as proposed by PvPI. Risk factor correlation was not studied. Thus, presence of other confounding factors which could have affected the final outcome of the study which were beyond the scope of current study remains a faint possibility.

Despite these limitations, our study has certain notable strengths. The ADR analysis was based on active surveillance of clinical and laboratory parameters. Moreover, there was minimal loss of data due to the prospective nature of the study.

This study focuses the importance of active ADR surveillance. ADR surveillance is an integral component of monitoring and evaluation in the ART program. The goal of monitoring is to detect the early toxicities and adverse effects to support the safe use of ART, thus improving the quality of care and treatment outcomes. Systematic and strong surveillance methods comprising structured pharmacovigilance systems assessing and monitoring safety profile and impact of antiretroviral drugs have thus been advocated.

**Conclusion**

The study enables to obtain information on the incidence and pattern of ADRs associated with various antiretroviral regimens in PLHIV, thereby reducing its occurrence and protecting the patient population from avoidable harm. Need of intensive monitoring for ADRs in ARTs thus seems to be a mandate. Patients education on ART-associated ADRs should be an important element of an effective HIV care package so as to facilitate reporting and subsequent management. Introduction of newer generation drugs with lesser toxicity profile in resource-limited settings is a prime mandate so as to ensure the provision of effective quality care to PLHIV.

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**Conflicts of interest**

There are no conflicts of interest.

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