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A study of the monitoring of the adverse drug reactions caused by antiretroviral drugs

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Abstract

Introduction: Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a disease of the human immune system. The drugs used in the treatment of HIV/AIDS are known to cause adverse effects, therefore this study was carried out for the monitoring and evaluation of adverse drug reactions (ADRs) caused by the use of antiretroviral drugs in patients of HIV/AIDS.

Methods: A prospective, observational, cross sectional study was done in Andaman & Nicobar Islands institute of medical sciences, to monitor ADRs caused by Antiretroviral therapy (ART) over a period of 10 months in 120 patients of HIV/AIDS. Out of 120 patients, 84 had ADR's. The data collected was filled in the spontaneous ADR reporting forms and Causality assessment was done using the WHO-UMC and Naranjo scale, seriousness was considered as per the ADR reporting form.

Results: The study shows that out of 84 patients with ADR's, 52 patients (61.9%) reported at least one ADR. 68 ADR's (80.9%) were attributed to the tenofovir + lamivudine + efavirenz regimen. Most of the ADRs were from the system organ class of neurological disorders as 55 patients (65.4%) and 16 patients (19%) were having gastrointestinal ADR's (19.44%) followed by Cutaneous ADR's in 5 patients (5.9%). Causality assessment by WHO-UMC scale revealed most of the reactions as 'possible' (99.2%) while Naranjo scale assessed most of them as 'probable' (69.8%).

Conclusion: Antiretroviral drugs have a huge potential for causing ADRs specially neurological and gastrointestinal. Active Pharmacovigilance is vital in recognizing such reactions to ensure timely management and optimal therapeutic outcomes.

Keywords: Antiretrovirals, Adverse Drug Reactions, Pharmacovigilance.

1. Introduction

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a disease of the human immune system. CD4 cells (T cells) are the target of this virus, thus making a person more likely to get other opportunistic infections. These opportunistic infections take a toll of the weakened immune system thus leading on to AIDS, which is known as the last stage of HIV infection.[1] Globally , HIV accounted for 1.1 million deaths occurring from HIV related causes in the year 2015.[2] India also is not lacking behind as in 2015, in India an estimated total of 21.17 lakh people were living with HIV, around 86 thousand total number of new HIV infections and 67.6 thousand deaths from AIDS-related causes.[3]

The management of HIV/AIDS includes the use of multiple drug therapy in the form of antiretroviral drugs. Highly active antiretroviral therapy (HAART) signifies the use of multiple drugs that act on different viral targets and are preferably prescribed as fixed-dose combinations (FDCs). Not to forget, antiretroviral drugs are associated with a wide range of adverse effects which led to non-

adherence to treatment by the patient and frequent treatment modifications. Nucleoside reverse transcriptase inhibitors (NRTIs) are one of the important components in the antiretroviral FDC regimens. Some of the notorious ADRs of NRTIs include zidovudine & Bone marrow suppression, stavudine & peripheral neuropathy, abacavir & hypersensitivity syndrome.[4] Tenofovir, is still to prove its long term safety, as there is a need for more data on its bone and renal toxicity profile.[5] Nevirapine and efavirenz belong to the category of Non-nucleoside reverse transcriptase inhibitors (NNRTIs). Some of the ADRs, attributed to the use of NNRTIs are Rashes, pruritus, elevated liver enzymes.[4]

To ensure the safety of anti-retroviral medicines used in the national AIDS control programme, the IPC (Indian Pharmacopeia Commission) and NACO formally agreed to collaborate by signing a Memorandum of Understanding (MoU).[6] Since not many studies have been done regarding the safety assessment of antiretroviral drugs being prescribed to patients in the state of Andaman & Nicobar islands, the present study was conducted in the year 2016-2017 to monitor the ADRs associated with the use of antiretroviral drugs being prescribed.

2. Materials and methods

A prospective observational study was carried out over a period of 10 months from October 2016 to august 2017 in Andaman & Nicobar Islands institute of medical sciences, Port Blair, India being the regional pharmacovigilance center in the state of Andaman & Nicobar Islands under PvPI. A total of 120 patients were included in the study, out of which 84 patients had one or more adverse drug reactions. This study enrolled the patients who were diagnosed as HIV positive and on antiretroviral treatment and the spontaneous reports of adverse events were recorded. Focus was laid on maintaining the confidentiality of the patients. Patients fulfilling the inclusion criteria and having none of the exclusion criteria were enrolled in the study. For the purpose of causality assessment the WHO-UMC [7] and the Naranjo scale [8] were used. Seriousness of the reaction was determined as per the ADR reporting form which considers the following reactions or reaction outcomes as serious: death, life threatening, hospitalization (initial/prolonged), disability, required intervention to prevent permanent impairment/damage and congenital anomaly. The data thus obtained was expressed in percentage & proportion and was analyzed accordingly using Microsoft excel software.

2.1 Inclusion criteria

1) All the patients of age group 18-65 years of either gender affected by HIV/AIDS.
2) Patients already on antiretroviral treatment.

2.2 Exclusion criteria

1) Pregnant females
2) Patients with past history of allergy to antiretroviral drugs and patients with life threatening complications or morbidities.
3) Patients with active Tuberculosis.

3. Observations

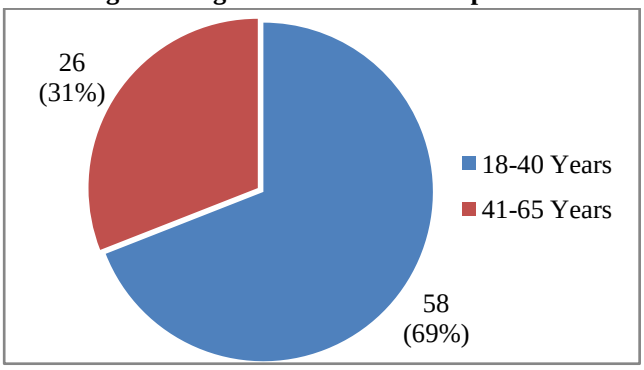
A total of 120 patients of already diagnosed with HIV/AIDS on anti-retroviral drugs were included in this study. Out of 120 patients, 84 patients had one or the other ADR following the treatment. Out of 84 patients, 48 (57.1%) patients were males and 36 (42.9%) patients were females with male: female ratio of 1.33:1 (**Table 1**).

Table 1: Distribution of patients with adverse drug reactions based on gender

S. No.	Gender of patients	No. of patients (84)	Percentage
1.	Male	48	57.1%
2.	Female	36	42.9%

A large number of the patients were in the age group of 18-40 years with 58(69%) patients in this age group, followed by 41-65 years age group with remaining 26(31%) patients. (**Figure 1**)

Figure 1: Age wise distribution of patients



Based on the WHO clinical staging of HIV-AIDS, 97.3% of the patients were characterized as clinical stage I with 2.7% as stage II. Table 1 shows the distribution pattern of ADRs with different FDCs of anti-retrovirals. The TDF+3TC+EFV regimen was most frequently prescribed in 116 (96.66% patients) and was responsible for ADRs in 81 patients (69.8%). (**Table 2**)

Table 2: Distribution of patient based on FDC'S of antiretrovirals

S. No.	Fixed dose combinations (FDCs)	No. of Patients	Total no. of ADR's Reported
1.	Tenofovir + Lamivudine +Efavirenz	**116**	**81**
2.	Zidovudine + Nevirapine + Tenofovir	**03**	**02**
3.	Tenofovir + Lamivudine + Nevirapine	**01**	**01**
Total		**120**	**84**

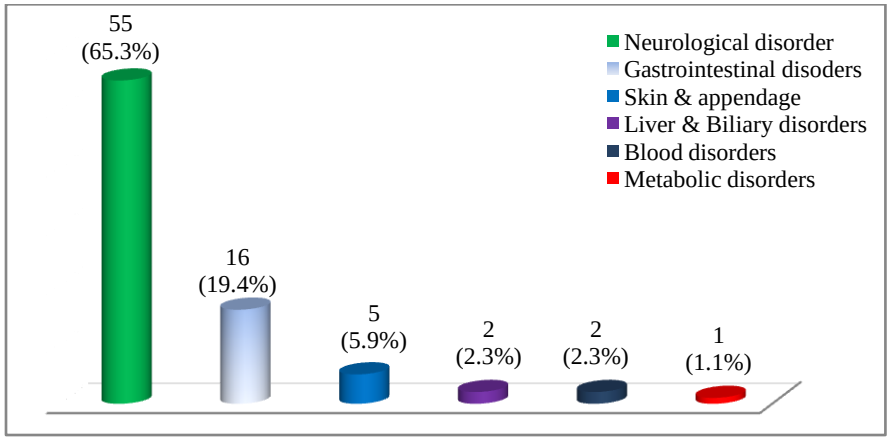
Taking each drug under consideration, it was observed that efavirenz was causally related to most number of ADRs. Out of the 116 prescriptions of efavirenz, 80(68.9%) ADRs were observed, followed by Tenofovir with 72(60%) ADR's, and the least number of ADR's caused by Zidovudine in 1(33.3%) patient out of 03 prescription in total. (**Table 3**)

Table 3: Distribution based on the ADR'S caused by individual drugs

S. No.	Individual Drug	No. of Prescriptions	No. of ADR's
1.	Efavirenz	116	80(68.9%)
2.	Nevirapine	04	02(50%)
3.	Zidovudine	03	01(33.3%)
4.	Tenofovir	120	72(60%)
5.	Lamivudine	120	18(15%)

In this study, the patients were divided based on the distribution pattern of ADRs according to the System Organ Class. Neurological disorders comprised of the number of ADRs (65.3%) followed by gastrointestinal disorders (19.4%) and skin and appendages disorders (5.9%), followed by Liver & Biliary disorders, Blood disorders, Metabolic & Nutritional disorders with (2.3%), (2.3%) & (1.1%) ADR's respectively. (**Figure 2**)

Figure 2: Distribution pattern of Adverse Drug Reactions (ADR's) according to System Organ Class (SOC)



In this study, sub-classification of different SOC disorders was done and their corresponding percentages were calculated. Dizziness (52.8%) was the most common reaction under the SOC of neurological disorders while nausea (31.2%) and rashes (80%) were the most frequently observed reactions under the SOCs of gastrointestinal and skin and appendages disorders respectively.

Table 4: Sub-classification of different SOC'S and corresponding ADR'S percentage

System Organ Class (No. of ADRs)	Adverse Drug Reaction	Number (%)
Neurological disorders (55)	Dizziness	29(52.8%)
	Sedation	18(32.7%)
	Irrelevant talking/Dreams	08(14.5%)
Gastrointestinal disorders (16)	Nausea	05(31.2%)
	Vomiting	03(18.8%)
	Flatulence	03(18.8%)
	Diarrhoea	04(25%)
	Gastritis	01(6.2%)
Skin and appendages disorders (5)	Rashes	04(80%)
	Pruritus	01(20%)
Liver and biliary disorders (2)	Raised liver enzymes and altered Biliary function	02(100%)
Blood disorders (2)	Cytopenia's	02(100%)
Metabolic and Nutritional disorders (1)	Raised Triglyceride levels	01(100%)

As per the WHO-UMC scale, the ADRs were categorized into 'certain', 'probable', 'possible' or 'unlikely'. 97% of the reactions were characterized 'possible' with 3% 'probable' reactions as per this scale. Using the Naranjo scale for causality assessment the ADRs were classified as 'definite', 'probable', 'possible' and 'doubtful'. Using this scale 66% reactions were deemed to be 'probable' in nature with 34% reactions as 'possible'.

4. Discussion

In the present study, out of the 120 patients, 84 patients (70%) reported adverse drug reactions, similar findings were seen in a study done by Kumar *et al*.[9] where 197 cases (55.34%) of ADRs were reported in 356 patients on ART and another study by Rajesh *et al*.[10] where 217 patients (48.2%) on combined antiretroviral regimens reported ADRs out of the 450 enrolled patients. However, in a study conducted by Shet *et al*.[11] 289 (90%) patients reported at least one ADR out of the 321 patients on first line antiretroviral therapy whereas Reddy *et al*[12] found a lower incidence in their study involving 300 patients with only 93 (31%) patients reporting at least one ADR while on ART. **(Table 5)**

Table 5: Comparison of present study with various other studies

Various Studies	Total no of patients	No of ADR's (% age)
Reddy *et al* [12]	356	197(55.34%)
Rajesh *et al*[13]	450	217(48.2%)
Shet *et al*[14]	321	289(90%)
Kumar *et al* [15]	300	93(31%)
Present study	120	84(70%)

The variations noted could possibly be attributed to factors like differences in the patient demographics, differences in the regimen prescriptions and ADR reporting practices within different centers, use of concurrent medications.

5. Conclusion

Antiretroviral drugs are the mainstay of the treatment of the patients of HIV/AIDS, on the contrary they also have a huge potential of causing adverse drug reactions. The TDF+3TC+EFV regimen prescribed as per the WHO and NACO guidelines can cause many ADRs. An active pharmacovigilance of the antiretroviral drugs must be carried out as it can be of help in prevention and management of the ADRs and thus ensure the safety of the patients.

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