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Adverse event monitoring of antiretroviral drugs- A pharmacovigilance perspective

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Abstract

Objective: To monitor and evaluate adverse drug reactions (ADRs) to antiretroviral drugs in patients of HIV/AIDS by active and spontaneous/solicited ADR monitoring.

Methods: A prospective observational study to monitor ADRs was carried out over 12 months in 187 patients of HIV/AIDS taking antiretroviral treatment. The ADRs reported were evaluated for incidence, frequency, causality, severity, seriousness and preventability. Causality assessment was done using the WHO-UMC and Naranjo scale, seriousness was considered as per the ADR reporting form, severity and preventability assessment were done as per the Hartwig severity scale and the modified Schumock and Thornton criteria respectively.

Results: 103 patients (55.1%) reported at least one ADR and 108 ADR reports were collected. Mostly the ADRs came from the tenofovir + lamivudine + efavirenz regimen with efavirenz related to most number of ADRs (52.5%). Maximum ADRs belonged to the system organ class of neurological disorders (64.81%) followed by gastrointestinal (19.44%) and skin and appendages disorders (7.40%). 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%). Most of the reactions (96.1%) were 'mild' in nature and no serious reactions were reported. Preventability assessment determined most reactions (94.6%) as 'not preventable'.

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. The virus attacks the CD4 cells (T cells), making a person more likely to get other infections or infection-related cancers. These opportunistic infections or cancers taking advantage of the weakened immune system lead on to AIDS, the last stage of HIV infection.[1] From a global perspective HIV remains a grave and a pertinent disease as 1.1 million deaths occurred from HIV related causes globally in the year 2015.[2] India in 2015, had total estimates of 21.17 lakh people living with HIV (PLHIV), 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 antiretroviral drugs. The use of multiple drugs that act on different viral targets is known as highly active antiretroviral therapy (HAART) and are preferably prescribed as fixed-dose combinations (FDCs). However, antiretroviral drugs are associated with a broad range of adverse effects which lead to poor patient adherence and frequent treatment modifications. Nucleoside reverse transcriptase inhibitors (NRTIs) find their place as the core components in the antiretroviral FDC regimens. Some characteristic ADRs of NRTIs include zidovudine induced bone marrow suppression, stavudine induced peripheral neuropathy and abacavir induced hypersensitivity

syndrome.[4] With tenofovir, there is concern over its long term safety with WHO identifying a need for more data on its bone and renal toxicity profile.[5] Nevirapine and efavirenz are the prescribed non-nucleoside reverse transcriptase inhibitors (NNRTIs) as per national AIDS control organization (NACO). Rash, pruritus, elevated liver enzymes, etc. are all well known ADRs with nevirapine while the most common adverse effects of efavirenz involve the central nervous system.[4] A need is therefore felt for proper monitoring of the treatment related ADRs or in other words 'pharmacovigilance'. The pharmacovigilance programme functions on the basis of national pharmacovigilance centers coordinated by the WHO programme for international drug monitoring, which consists of the WHO collaborating centre for international drug monitoring, Uppsala and the pharmacovigilance department of WHO, Geneva.[6] India formally became a member of the WHO programme in 1997 [7] and in July 2010 and under the aegis of health ministry a nation-wide ADR monitoring programme was launched under the title of pharmacovigilance programme of India or PvPI.[8] 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).[9] Since not many studies have been done regarding the safety assessment of antiretroviral drugs being prescribed to patients in the state of Haryana, the present study was planned to monitor the ADRs associated with the first line antiretroviral drugs being prescribed in our institution.

2. Material and Methods

A prospective observational study was carried out in which spontaneous/solicited reports of adverse events were recorded in the patients diagnosed to be HIV positive and on antiretroviral treatment. The study was conducted by the Department of Pharmacology, Pt. B.D. Sharma PGIMS, Rohtak, being the regional pharmacovigilance center in the state of Haryana under PvPI, in collaboration with the ART centre at PGIMS, Rohtak, which is a NACO representative centre. No fresh intervention was done and the confidentiality of the patients was duly maintained. The study was done in accordance with the principles of Good Clinical Practice (GCP) and declaration of Helsinki.

Patients found eligible based on the predefined inclusion and exclusion criteria were considered for enrollment in the study. Inclusion criteria consisted of all the patients of age group 18-65 years of either gender affected by HIV/AIDS who were either treatment naive and/or recently recruited and already on antiretroviral treatment. Pregnant females who fulfilled the above mentioned criteria were also included. Exclusion criteria constituted patients of HIV/AIDS who belonged to clinical stage III or IV according to the WHO clinical staging of HIV/AIDS, patients who were on treatment for tuberculosis and/or HBV/HCV infection, patients with past history of allergy to antiretroviral drugs and patients with life threatening complications or morbidities.

The study was conducted over a period of 12 months in a total of 187 patients diagnosed with HIV/AIDS. Patient's data like demographics, clinical stage, CD4 count, treatment regimen prescribed, concomitant drugs, laboratory investigations, whether ADR reported or not, etc. were filled up into patient's case record form (CRF). The ADRs reported were duly filled up in the suspected adverse drug reaction reporting form of Central Drugs Standard Control Organization (CDSCO) and the ADR was put to further assessment for its causality, seriousness, severity and preventability.

For the purpose of causality assessment the WHO-UMC[10] and the Naranjo scale[11] 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 Hartwig severity scale developed by Hartwig *et al*.[12] was used for determining the severity of the observed adverse reactions. Preventability of the ADRs was assessed by modified Schumock and Thornton criteria.[13]

2.1 Statistical Methods: Descriptive statistical analysis was used with data expressed as numbers and percentages. All statistical analysis was carried out using Microsoft excel and the IBM SPSS statistics version 20.0. The analysis was performed in a step wise manner by suitable categorization of the various observations made.

3. Results

A total of 187 patients of HIV/AIDS on anti-retroviral drugs were included in this study. Both the genders were more or less equally represented with 52.4% female and 47.6% male patients. A large number of the patients belonged to the age group of 18-40 years (74.9%) with remaining 47 patients (25.1%) belonging to the age group of 41-65 years. 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. Considering CD4 counts, 129 (68.98%) patients had a CD4 count of $\geq$ 200 while 58 (31.02%) patients had CD4 count of <200. Out of the 187 patients, 103 patients (55.1%) had adverse drug reactions and a total of 108 ADR reports were collected. Table 1 shows the distribution pattern of ADRs with different FDCs of antiretrovirals. The TDF+3TC+EFV regimen was most frequently prescribed (96.79% patients) and produced ADRs in 100 patients (55.24%).

Table 1: Distribution pattern of ADRs in patients on different FDCs of antiretrovirals

Fixed dose combinations (FDCs)	Number of patients (total =187)	Patients with ADRs	Total number of ADR reports
TDF+3TC+EFV	181 (96.79%)	100 (55.24%)	104
AZT+3TC+NVP	5 (2.6%)	2 (40%)	3
TDF+3TC+NVP	1(0.5%)	1(100%)	1

TDF: Tenofovir; 3TC: Lamivudine; EFV: Efavirenz; AZT: Zidovudine; NVP: Nevirapine

Taking each drug under consideration (Table 2) it was observed that efavirenz was causally related to most number of ADRs. Out of the 181 prescriptions of efavirenz, 95 ADRs (52.48%) were observed. Nevirapine was next in line causing 3 ADRs (50%) in 6 prescriptions.

Table 2: Distribution pattern of ADRs observed with individual drugs

Drug	Number of Prescriptions	Related ADRs
Efavirenz	181	95(52.48%)
Nevirapine	6	3(50%)
Zidovudine	5	1(20%)
Tenofovir	182	23(12.63%)
Lamivudine	187	7(3.74%)

The ADRs were also classified based on the System Organ Class (SOC) of World Health Organization-Adverse Reaction Terminology (WHO-ART). Considering the number of ADRs in a certain SOC caused by a particular drug vis-à-vis the number of drug prescriptions (Table 3), it was observed that in all the prescriptions of tenofovir, the maximum number of ADRs i.e. 18 ADRs (9.9%) were of gastrointestinal origin. The SOC of neurological disorders was chiefly affected in patients on efavirenz with 70 (38.7%) cases of neurological disorders recorded.

Table 3: System Organ Class involvement and drug prescriptions as per WHO-ART

No. of prescriptions SOC involved	Tenofovir (182)	Lamivudine (187)	Efavirenz (181)	Zidovudine (5)	Nevirapine (6)
Neurological disorders	0	0	70(38.7%)	0	0
Gastrointestinal disorders	18(9.9%)	3(1.6%)	15(8.3%)	0	0
Skin and appendages disorder	1(0.5%)	1(0.5%)	6(3.3%)	0	2(33.3%)
Liver and biliary disorders	0	0	2(1.1%)	0	1(16.7%)
Blood Disorders	0	0	0	1(20%)	0
Metabolic and nutritional disorders	0	0	1(0.5%)	0	0
Urinary tract disorders	1(0.5%)	0	0	0	0
Body as a whole-general disorders	3(1.6%)	3(1.6%)	1(0.5%)	0	0

Figure 1 shows the distribution pattern of ADRs according to the System Organ Class. Neurological disorders comprised of the number of ADRs (64.81%) followed by gastrointestinal disorders (19.44%) and skin and appendages disorders (7.40%).

Figure 1: Distribution pattern of adverse drug reactions (ADRs) according to System Organ Class (SOC)

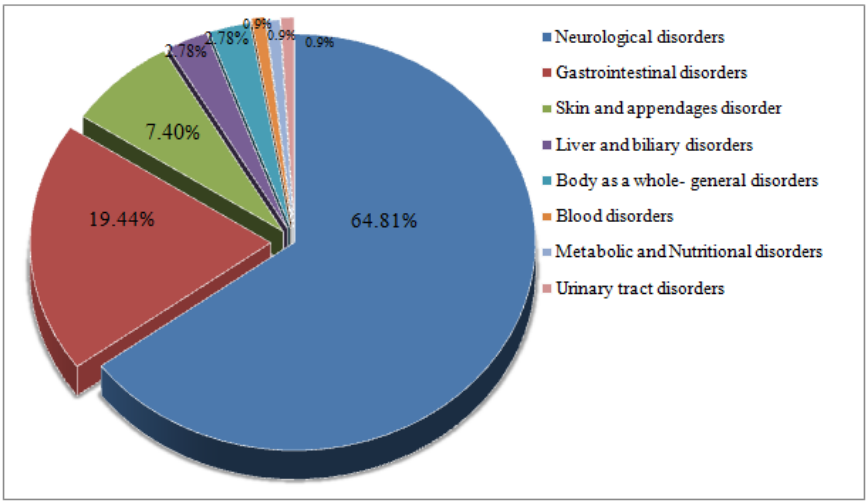

Table 4 shows sub-classification of different SOC disorders and corresponding percentages. Dizziness (74.3%) was the most common reaction under the SOC of neurological disorders while diarrhea (42.9%) and rash (87.5%) were the most frequently observed reactions under the SOCs of gastrointestinal and skin and appendages disorders respectively.

Table 4: Sub-classification of different SOCs and corresponding ADR percentage

System Organ Class (No. of ADRs)	ADR	Number (%)
Neurological disorders (70)	Dizziness	52(74.3%)
	Sedation	15(21.4%)
	Vivid Dreams	3(4.3%)
Gastrointestinal disorders (21)	Diarrhoea	9(42.9%)
	Flatulence	5(23.8%)
	Vomiting	4(19%)
	Gastritis	2(9.5%)
	Nausea	1(4.8%)
Skin and appendages disorders (8)	Rash	7(87.5%)
	Pruritus	1(12.5%)
Liver and biliary disorders (3)	Elevated Liver Enzymes	3(100%)
Body as a whole- general disorders(3)	Fatigue	2 (66.7%)
	Fever	1 (33.3%)
Blood disorders (1)	Reduced Counts	1(100%)
Metabolic and Nutritional disorders (1)	Raised Triglycerides	1(100%)
Urinary tract disorders (1)	Raised Serum Creatinine	1(100%)

Table 5 shows the distribution pattern of ADRs in various SOCs with respect to number of regimen prescriptions. Of the 181 total prescriptions of TDF+3TC+EFV regimen, 70 (38.7%) neurological reactions were observed. The other significant reactions with this regimen belonged to the SOC of gastrointestinal disorders (11.6%) and skin and appendages disorders (3.3%). In the 5 prescriptions of AZT+3TC+NVP regimen, three reactions, one each in the SOC of skin and appendages disorders (20%), liver and biliary disorders (20%) and blood disorders (20%), were observed.

Table 5: Distribution pattern of ADRs in various SOCs with respect to the number of the regimen prescriptions

Regimen (No. of prescriptions) SOC	TDF+3TC +EFV (181)	AZT+3TC+ NVP (5)	TDF+3TC+ NVP (1)
Neurological disorders	70 (38.7%)	0	0
Gastrointestinal disorders	21 (11.6%)	0	0
Skin and appendages disorders	6 (3.3%)	1(20%)	1(100%)
Liver and biliary disorders	2 (1.1%)	1 (20%)	0
Blood disorders	0	1(20%)	0
Metabolic and nutritional disorders	1 (0.5%)	0	0
Urinary tract disorders	1 (0.5%)	0	0
Body as a whole- general disorders	3 (1.6%)	0	0

Based on the WHO-UMC scale the ADRs were categorized into 'certain', 'probable', 'possible' or 'unlikely'. 99.2% of the reactions were characterized 'possible' with 0.8% '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 69.8% reactions were deemed to be 'probable' in nature with 30.2% reactions as 'possible'.

No serious reactions were recorded during the period of the study. Based on the Hartwig severity scale to assess the severity of the individual ADRs, most of the reactions were found to be 'mild' in nature (96.1%), with few 'moderate' (3.9%) and no 'severe' reactions.

Based on the modified Schumock and Thornton criteria, overall, most of the ADRs were found to be 'not preventable' (94.6%), while few belonged to 'definitely preventable' (5.4%) category and none to 'probably preventable' category.

4. Discussion

In the present study, out of the 187 patients, 103 patients (55.1%) reported adverse events and a total of 108 ADR reports were collected. The findings are in tune with a study by Kumar *et al*.,[14] where 197 cases (55.34%) of ADRs were reported in 356 patients on ART and another study by Rajesh *et al*.,[15] 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*.,[16] 289 (90%) patients reported at least one ADR out of the 321 patients on first line antiretroviral therapy whereas Reddy *et al*.,[17] found a lower incidence in their study involving 300 patients with only 93 (31%) patients reporting at least one ADR while on ART. 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 and presence of co-morbidities.

Efavirenz caused ADRs in maximum (52.48%) number of cases. Sharma *et al*.[18] reported an incidence of efavirenz related ADRs to be 45.4%. Efavirenz was also the single leading cause of ADRs amongst all the antiretroviral drugs in a study by Kumar *et al*.[14]

Out of the 6 prescriptions of nevirapine, 50% of the patients developed ADRs. 1 ADR in a patient (20%) was found to be zidovudine related. About 18% incidence of adverse effects with nevirapine and 50% with zidovudine was observed in a ADR monitoring study.[18]

The neurological disorders comprised of most number of ADRs (64.81%) followed by gastrointestinal disorders (19.44%) and skin and appendages disorders

(7.40%). Neuropsychiatric adverse events (29.44%) were also the most common ADRs in a study from Ranchi by Kumar *et al*.,[14] followed by gastrointestinal and hepatobiliary system (24.87%). An ADR monitoring study of antiretrovirals from Guwahati reported the maximum (31.25%) ADRs to be gastrointestinal system related followed by skin (23.75%) and central nervous system (16.25%) related ADRs.[17] High incidence of neurological involvement observed in this study can be attributed to the drug efavirenz which has a well known and documented property of causing neuropsychiatric afflictions.[19] Hence, the neurological, the gastrointestinal and the cutaneous system toxicities are most common with antiretrovirals.

Amongst the neurological disorders, dizziness was the most common adverse reaction observed (74.3%), followed by sedation (21.4%) and vivid dreams (4.3%). Reddy *et al*.[17] too found dizziness to be the most common central nervous system ADR with antiretrovirals with 11 (42%) cases out of the total 26 central nervous system ADRs. Diarrhea was the most frequent ADR under the heading of gastrointestinal disorders with 9 (42.9%) ADRs. A similar study from Delhi reported gastrointestinal system ADRs as most common with antiretrovirals, manifesting as loss of appetite (24.8%), dyspepsia (21.7%), abdominal discomfort (14.1%) and diarrhea (11.8%).[20] Under the skin and appendages disorders, rash was the most common ADR (87.5%) followed by prutitus (12.5%). Nagpal *et al*.[20] found 55 (96.5%) reactions of skin rash and itching (considered together) of the 57 cutaneous reactions to antiretrovirals.

All the ADRs belonging to the SOC of neurological disorder occurred in the TDF+3TC+EFV regimen and were found to be related to the drug efavirenz. It has been determined in western cohorts that 50% of patients have neurological complaints within a month of initiation of efavirenz.[21] We too discovered a similar temporal pattern of neurological adverse effects, specially dizziness, occurring upon initiation of efavirenz but gradually subsiding over a period of 3-4 weeks.

Gastrointestinal disorders also occurred primarily with the TDF+3TC+EFV regimen. Tenofovir, efavirenz and lamivudine were all determined responsible for the disorders of this particular SOC. Gastrointestinal events such as diarrhea and nausea have been reported in the clinical trials with tenofovir.[22] 7.6% reactions of gastrointestinal in origin were recorded with efavirenz in a study from India by Shet *et al*.[16]

The maximum incidence of skin and appendages disorders was observed in the TDF+3TC+NVP and the AZT+3TC+NVP regimen, attributed to the drug nevirapine. Around 16% of patients on nevirapine develop a mild to moderate maculopapular rash, within the first 6 weeks on therapy.[23]

The incidence of liver and biliary disorders was most with the AZT+3TC+NVP regimen and they were nevirapine related. These reactions were three cases of hepatic enzyme elevation with an incidence of 16.7%. A study by Law *et al*.[24] observed a 18.6% incidence of hepatitis in patients taking nevirapine.

The causality assessment scale with WHO-UMC revealed 99.2% reactions to be of 'possible' in nature with 1 (0.8%) case deemed 'probable'. Nagpal *et al*.[20] too established most of the reactions with antiretrovirals to be of 'possible' in nature (93.3%) using the WHO-UMC scale. Causality assessment based on the Naranjo scale revealed 69.8% reactions to be 'probable' in nature and 30.2% reactions as 'possible'. Jha *et al*.,[25] using the Naranjo scale, revealed 66.04% reactions with antiretrovirals as 'probable' and 33.96% as 'possible'.

The Hartwig severity scale determined most of the reactions (96.1%) to be 'mild' in nature with few moderate reactions (3.9%). No 'severe' reactions were observed. Kumar *et al*.[14] also employed this scale for severity assessment of ADRs with antiretrovirals and found 67.51% reactions as 'mild', 29.44% reactions as 'moderate' and 3.04% reactions as 'severe'.

Most of the ADRs observed in our study (94.6%) belonged to the 'not preventable' category. 7 cases (5.4%) belonged to the 'definitely preventable' category. Kumar *et al*.[14] have earlier reported 41.12% reactions with ARVs as 'not preventable', 37.06% as 'probably preventable' and 21.82% as 'definitively preventable' reactions while Rajesh *et al*.[15] documented 40.4% reactions as 'not preventable' with 30.9% 'probably preventable' and 28.7% 'definitively preventable' reactions.

5. Conclusion

Antiretroviral drugs though, the mainstay of the treatment of the patients of HIV/AIDS, yet have a huge potential for causing adverse drug reactions mostly affecting the nervous system and the gastrointestinal tract. The TDF+3TC+EFV regimen prescribed as per the WHO and NACO guidelines can cause many ADRs, specially with efavirenz. An active pharmacovigilance of the antiretroviral drugs must be carried out as it can go a long way in prevention and management of these ADRs and thus ensure not only the safety of the patients but compliance to the treatment which is necessary for optimal therapeutic outcomes.

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