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Assessment of adverse drug reactions to antiretroviral agents among HIV patients

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ABSTRACT

Objective: The objective of the study was to determine the causality, predictability, preventability and severity of Adverse Drug Reactions (ADRs) among Human Immunodeficiency Virus (HIV) positive patients who are on Highly Active Antiretroviral Therapy (HAART). **Method**: All spontaneous ADRs to Anti Retroviral Agents were collected over a period of three years (July 2012–June 2015) from two Anti Retroviral Therapy (ART) centers in Mysore city, Karnataka. Predictability was assessed based on previous history on exposure to the drug or literature incidence of ADRs, preventability was assessed by using modified Schumock and Thornton scale, causality was assessed by WHO probability scale and severity was assessed by using modified Hartwig and Siegel Scale. **Results**: A total of 1120 ADRs were documented in the study period. Majority (94.5%) of reactions were predictable. However, 72.5% of reactions were preventable (29.5% definitely preventable, 43% probably preventable). Among all the reactions, only 34.8% was assessed to be mild and 6.4% of reactions were severe. On causality assessment 74.5% of ADRs were found to be probable in nature. **Conclusion**: Majority of the ADRs in HIV patients are predictable and many of these reactions may also be preventable. Even though, we may not be able to prevent all predictable ADRs, the goal should be to increase awareness on ADRs and encourage early detection and intervention by conducting similar studies in understanding the ADRs and to minimize patient discomfort which results in medication non-adherence.

INTRODUCTION

Human Immunodeficiency Virus (HIV) continues to be a major global public health issue. In 2016, an estimated 36.7 million people were living with HIV (including 1.8 million children) – with a global HIV prevalence of 0.8% among adults. There were roughly 1.8 million new HIV infections occurred in 2016, a decline from 2.1 million new infections in 2015 (www.avert.org). India has the third largest HIV epidemic in the world with 2.1 million people living with HIV (PLHIV) in 2016. Children (<15 years) account for 6.54%, while two fifth (40.5%) of total HIV infections are among females. It was estimated that 1.3 million PLHIV in India needed ART in 2015 (www.NACO.org.in). The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in Acquired Immunodeficiency Syndrome (AIDS) related morbidity and mortality. In India, efforts of National AIDS Control Organization (NACO) to make available, the generic HAART, to HIV infected individuals, at no cost, has enormously increased the access to ARVs to the poor and needy (www.unaids.org).

The adverse effects of HAART are of serious concern as it may negatively affect the confidence in treatment resulting in decreased medication adherence (Srikanth *et al*., 2012). Hence, the safe and effective management of HIV infection also requires understanding of adverse drug reactions (ADRs) associated with HAART. Data obtained from the clinical trials regarding drug related adverse events in HIV positive patients has many limitations as this data includes selected and homogenous populations under well controlled conditions. On the other hand, most of the clinical trials including randomized studies evaluated only the efficacy of ARVs but were unable to detect rare and severe side effects. However, observational studies widely documented that ART

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induced ADRs has significant impact on the patients quality of life and adherence to ART (Rolfes *et al*., 2016; Rita *et al*., 2017).

There are limited numbers of studies conducted in India to intensively monitor the hospitalized HIV positive patients for possible ADRs and systematic documentation of the findings to analyze these ADRs. Hence, present study is designed to determine the prevalence, causality, predictability, preventability, and severity of ADRs among HIV patients admitted in two South Indian ART centers.

MATERIALS AND METHODS

This was a hospital based retrospective observational study conducted at two HIV care clinics in Mysore, Karnataka from July 2012-June 2015. All the spontaneous adverse drug reactions reported to fixed dose of HAART were included in the study. The study was approved by an institutional ethical committee of the study sites. Confidentiality of the information was assured in a way that no disclosure of any name of the patient or health care provider in relation to the finding was made. Patient and ADR related information was collected from the ADR reporting forms and patient case records. ADRs due to the medications used for treating the opportunistic infections and co-morbid conditions were excluded. Collected information on ADRs was reviewed by clinical pharmacists at the study site, further assessed in consultation with the study site treating physicians and was documented.

The preventability was determined by using modified criteria adopted from Schumock and Thornton. Any answer of "yes" to any question suggests that the ADR might have been preventable in having any allergy or previously documented similar type of reaction, inappropriate drug was chosen to patient condition or chosen dose, route and frequency of administration is in-appropriate to patient age or weight. Along with these it was also considered to be preventable if a toxic serum drug concentration was documented or any known treatment available for the occurred adverse drug reaction. ADRs are also considered to be probably preventable if any drug-drug interaction was cause for ADR, not performing the necessary lab tests, poor medication adherence is the cause for ADR or any possible preventive measures were not administered to the patient. Answering no to above all was considered to be non-preventable reaction (Schumock and Thornton, 1992).

Severity of a reaction was assessed by using Hartwig *et al*. scale and classified as mild, moderate and severe. ADRs are considered to be severe if patient outcomes fall in category permanent harm, lead to death and required any intensive medical care admission due to ADR. ADRs are considered to be moderate if withdrawal of suspected drug therapy was required, needing antidote, and lead to increase the hospital stay or reason for admission. Finally ADRs were classified to be mild if it doesn't require any change in the treatment or not requiring antidote (Hartwig *et al*., 1992). The predictability was determined by incidence rate obtained from the literature considered to be predictable if incidence rate is more than 1% and also on previous allergy history of ADRs. The causality assessment of all ADRs was performed by using WHO probability scale in identifying the causal relationship associated and were categorized accordingly among the six categories. Further, all the ADRs observed were grouped on the basis of system organ class on which they affected (Meyboom *et al*., 1997).

RESULTS AND DISCUSSION

A total of 1120 ADRs were reported in 860 patients (male 497, female 364). Majority (94.5%) of reactions were predictable. Findings from this study in terms of predictability were similar to the study published earlier where 96.1% of the ADRs were reported as predictable (Modayil *et al*., 2010). Reactions such as pancreatitis, depression, Steven Johnson's Syndrome was not predictable and was less than 5% of total reports amongst the study population.

Among all the reactions, 331 (29.5%) ADRs were "definitely preventable", 489 (43%) were "probably preventable" while remaining 300 (27.5%) were "not preventable" reactions. Hepatotoxicity was observed in study patients who were mainly on nevirapine based therapy. Liver enzyme levels (AST, ALT) were raised in these patients up to 2-3 folds from the normal value. Positive rechallenge was observed in our study patients to nevirapine and in many patients the drug was withdrawn and all patients recovered from the ADRs. Hepatitis was predictable and was seen with Non-nucleoside reverse transcriptase inhibitors (NNRTIs) class of drugs. However, while an ADR occurred, same class of drug was substituted due to limited access to second line regimen. Regular monitoring of liver enzymes in the patients initiated with NNRTIs might help in the early detection and prevention of occurrence of these reactions.

Gastrointestinal system disorders 19.75% (221) were observed in patients on zidovudine containing regimen after first few weeks of therapy and symptoms were self-limiting. The gastrointestinal system disorders were the reason for medication non-adherence in a study conducted by (Carr., and Cooper., 2000). However, they are preventable by educating the patients to take zidovudine with food and avoid the intake of zidovudine along with carbonated and caffeinated drinks.

Central and peripheral nervous system (CNS) disorders 10.62% (119/1120) like dizziness and peripheral neuropathy were observed in our study. Efavirenz and stavudine based regimens were mainly implicated in causing this CNS disorders. Peripheral neuropathy 5.8% (66) cases were observed in patients who were on stavudine containing regimen for more than six months. In all the cases, definite improvement was observed after discontinuation of stavudine. In addition to this dechallenge, pyridoxine was given to treat peripheral neuropathy in patients with severe condition. Majority of the patients complained of dizziness during night time. Dizziness may probably due to the administration of efavirenz at night. Symptoms were observed in the first two weeks of therapy and were self-limiting. A longitudinal study by (Fumaz *et al*., 2005) showed increased risk of experiencing CNS toxicity in the first two weeks of therapy. There was significant association between CNS toxicity and the efavirenz plasma levels. Administration of cinnarizine, an antihistamine along with efavirenz containing regimen may help in preventing/reducing severity of dizziness.

In our study anaemia 29.10% (326) was the most commonly observed ADR due to zidovudine + lamivudine + nevirapine/efavirenz regimen. This was probably a preventable reaction. Anaemia occurred (haemoglobin < 7 g/dl) within the first few months of initiation of therapy. In majority of the patients,

improvement in haemoglobin level was observed once zidovudine containing regimen was withdrawn which was similar to the study conducted by (Kaibalya, *et al*. 2015). So, the red blood cell disorders could have been minimized by regular monitoring of blood parameters. It is also advised not to start zidovudine in patients with haemoglobin less than 8 g/dl. However, implementation of such strategy may be difficult in a resource limited settings.

Some of the reactions like rash, urticaria of skin and appendages (10.62%) and musculo-skeletal disorders like myalgia (1.9%) were assessed to be not preventable. This probably indicates that good number of ADRs may occur even with implementation of some of the preventive measures.

Severity criteria assessment showed 390 (34.8%) of the reactions were mild in nature whereas 659 (58.8%) of the reactions were considered moderate and 71 (6.4%) of the reactions were classified as severe in nature (Figure 1). Severe reactions were about 1% in our study population though no fatality was observed. About 34% of ADRs were reason for both hospitalization and for prolongation of hospitalization. Severe reactions found in our study were lactic acidosis, lipodystrophy and nail discoloration. The severity assessment carried out showed that 35% of the reactions was mild and in almost all these patients complete recovery was observed requiring no changes in the regimen. Very few ADRs were severe enough to necessitate the switchover to other regimen. Nevirapine induced Steven Johnson Syndrome was observed in patients receiving the Zidovudine + Lamivudine + Nevirapine regimen. These patients were hospitalized, dechallenged and substituted with other NNRTIs. Stavudine induced lipodystrophy also necessitated substitution of non stavudine based regimen. Reactions which were moderate in nature were managed by symptomatic treatment alone without changing the regimens.

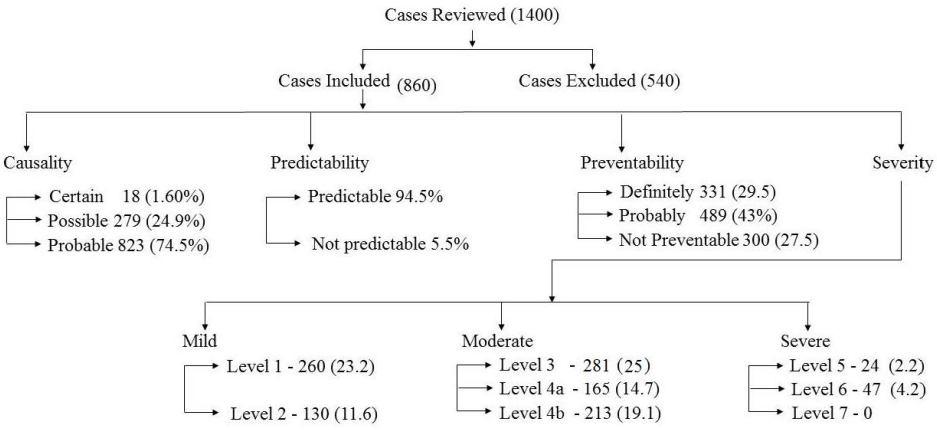

Fig. 1: Flow chart presentation of assessment of ADRs.

An epidemiological research conducted in India and Brazil on patients receiving ART revealed the occurrence of ADRs as 25.5% and 34.5%, respectively (Diwakar *et al*., 2012). A study by (Shet *et al*., 2014) clearly showed that adverse effects of various antiretrovirals were one of the major reasons for the treatment change.

The causality of the ADRs was evaluated and was found to be 823 (74.5%) of reactions are probable whereas 279 (24.90%) were possible and 18 (1.60%) were definite in nature. IRIS 9.28% (104) was seen among study patients to ART regimens included both paradoxical and unmasking IRIS. In majority of the patients IRIS manifested as TB. IRIS presents challenges to the clinician in terms of diagnosis, management, decisions to continue ART, and, if ART need to be continued, motivating patients to adhere to the therapy despite symptom deterioration. These challenges are further compounded by the lack of both a diagnostic test and an evidence based guidelines for the management of IRIS. Similar findings were observed in a study from (Pramod *et al*., 2016).

Some reactions such as acute renal failure (ARF) 1.7% observed to TDF based regimen, were probable in nature. So, TDF was substituted with other NRTI and reaction was reversible in majority of patients after cessation of the drugs. Among the patients who developed peripheral neuropathy, stavudine was withdrawn and a definite improvement was observed. This finding suggests that stavudine was attributed to the occurrence of peripheral neuropathy which is similar to study conducted and its establishment shown by (Reddy *et al*., n.d.). Stavudine was also found to cause majority of metabolic and nutritional disorders such as lipodystrophy in patients who received for more than two years which needed the substitution of this drug.

Table 1: Regimen implicated in ADRs.

Regimen	Number (%) [n = 1120]
Zidovudine + Lamivudine + Nevirapine	586 (52.32)
Zidovudine + Lamivudine + Efavirenz	145 (12.94)
Stavudine + Lamivudine + Nevirapine	202 (18.03)
Stavudine + Lamivudine + Efavirenz	103 (9.19)
Tenofovir + Lamivudine + Nevirapine	38 (3.39)
Tenofovir + Lamivudine + Efavirenz	35 (3.12)
Tenofovir + Lamivudine + Atazanavir/ritonavir	07 (0.62)
Stavudine + Lamivudine + Atazanavir/ritonavir	04 (0.35)

About 52.3% of reactions were attributed to zidovudine + lamivudine + nevirapine regimen followed by 18.2% due to stavudine + lamivudine + nevirapine regimen, others regimens implicated in ADRs are shown in Table 1. The system organ class which affected most was red blood cell disorder 29.10% followed by gastrointestinal disorder 19.73% and details pertaining to other system organ class are shown in Table 2.

There were few limitations in our study. Firstly, as it is a retrospective study, we couldn't follow the patients for the prognosis of ADRs. Also because of irregular clinic attendance by patients, our study may underestimate the incidence of ADRs to ART. Secondly, limited access to laboratory facilities may also have contributed to under-recognition of ADRs those are identified based on lab reports.

Table 2: System organ class affected by reported ADR.

System Organ Class (WHO ART SOC code)	Type of ADRs	Number of ADRs (%) [n = 1120]
Red blood cell disorder (1210)	Anaemia (326)	326 (29.10)
Metabolic and nutritional disorder (0800)	Lactic Acidosis (58), Lipodystrophy (25)	83 (7.41)
Central and peripheral nervous system (0410)	Headache (6), Dizziness (47), Peripheral Neuropathy (66)	119 (10.62)
Gastrointestinal system disorders (0600)	Vomiting (158), Diarrhoea (18), Gastritis (44), Pancreatitis (01)	221 (19.73)
Liver and biliary system disorder (0700)	Hyperbilirubinemia (7), Increased Liver Function Tests (50)	57 (5.08)
Psychiatric Disorders (0500)	Insomnia (18), Depression (6)	24 (2.14)
Skin and appendages disorders (0100)	Hyperpigmentation (04), Rash (66), SJS (10), Itching (39)	119 (10.62)
Urinary system disorders (1300)	Acute Renal Failure (20), Fancouni Syndrome (4)	24 (2.14)
White cell and RES disorders (1220)	Leucopenia (13)	13 (1.21)
Body as a whole general disorders (1810)	Fatigue (5), Hypersensitivity (3)	08 (0.71)
Resistance Mechanism disorder (1830)	Immune Reconstitution Inflammatory Syndrome (104)	104 (9.28)
Musculo-Skeletal disorder (0200)	Myalgia (22)	22 (1.96)

CONCLUSION

With the increasing access to use of HAART it is possible that there is an increased risk of drug induced illness due to HAART. As observed in this study many ADRs are predictable and possibly preventable. Early detection and management of ADRs will reduce the economic burden and improve the medication adherence resulting in better therapeutic outcomes.

CONFLICTS OF INTEREST

None to declare.

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