Research Article

A Study on Adverse Drug Reactions of Anti-Retroviral Therapy in HIV Patients

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ABSTRACT

Human immunodeficiency virus (HIV) is a blood-borne virus caused by HIV-1 or HIV-2 retroviruses. Highly active antiretroviral therapy (HAART) is the treatment for preventing immune deterioration, which includes nucleoside reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs). This study is a retrospective study using the data of 203 patients with HIV receiving HAART (2012-2014) admitted in the emergency medicine department of Amrita Institute Of Medical Sciences Kochi. According to the study, out of 203 patients, 55 patients were found to have 61 Adverse Drug Reaction (ADR). Based on the ADR 40.98% were found to have anemia, 8.19% have bone marrow suppression, 6.55% have central nervous system side effects, 6.55% have dyslipidemia, 6.55% have liver enzyme elevation, 1.63% have urticaria, 8.19% patients have peripheral neuropathy, 1.63% have microhematuria and 1.63% patients had discoloration of nails. Hematological and dermatological systems were most affected by adverse drug reaction and is mainly caused by Zidovudine. Stavudine causes Lipodystrophy, Peripheral neuropathy and Urticaria. Dyslipidemia is caused by Ritonavir. CNS effects such as decreased sleep and abnormal dreams are caused by Efavirenz. While Atazanavir and Efavirenz causes liver function test elevation. 65.21% of patients with ADR's needed withdrawal of the implicated drug. The most frequent ADR recognized in this study is induced by Zidovudine included reactions such as anemia, Lipodystrophy, black coloration of nails, hematuria and bone marrow suppression. Affected patients were treated with iron supplements, blood transfusion or the offending drug was withdrawn. Other common ADR's noted are LFT elevation, urticaria, dyslipidemia, CNS effects and microhematuria induced by other anti-retroviral drugs.

Keywords: Human Immuno deficiency Virus (HIV), Acquired Immune Deficiency Syndrome (AIDS), Highly Active Anti Retro Viral Therapy (HAART), Anti Retro Viral Therapy (ART), Adverse Drug Reactions (ADR).

INTRODUCTION

Highly active antiretroviral therapy (HAART; a combination of at least three drugs) for HIV-1 infection has led to substantial reductions in morbidity and mortality, Many HAART regimens result in near-complete suppression of HIV-1 replication. HAART is now the standard-of-care therapy[1]. Presently drugs belonging to classes of nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease Inhibitors, entry Inhibitors - CCR5 co-receptor antagonist and HIV integrase strand transfer inhibitors are Zidovudine, Stavudine Didanosine, Abacavir, Tenofovir, Efavirenz, Nevirapine, Etravirine, Atazanavir, Indinavir, Lopinavir, fosamprenavir, Enfuvirtide, Maraviroc, Raltegravir respectively. Two NRTIs are often combined with one medication from either of the two remaining classes, the nonnucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs)[2].

Nucleoside and monophosphorylated nucleotide-analogue reverse-transcriptase inhibitors (NRTIs and NtRTIs, respectively) are both phosphorylated intracellularly to active triphosphate forms, and are then incorporated into new DNA strands synthesized by HIV reverse transcriptase. The lack of a 3-hydroxyl group in NRTIs and NtRTIs results in HIV DNA chain termination. The major toxicities of NRTI and NtRTI therapy, particularly over the medium-term to long-term, are thought to be secondary to inhibition of mitochondrial DNA polymerase, resulting in impaired synthesis of mitochondrial enzymes that generate ATP by oxidative phosphorylation. These include myopathy (Zidovudine); neuropathy (Stavudine, Didanosine, Zalcitabine); hepatic Steatosis and lactic acidaemia (Didanosine, Stavudine, Zidovudine); and possibly also peripheral lipoatrophy (possibly all NRTIs, although predominantly with Stavudine); and pancreatitis (Didanosine)[1]. Patients with Zidovudine induced myopathy and NRTI-induced peripheral neuropathy have been shown to have reduced concentrations of L-carnitine. All licensed non-nucleoside reverse transcriptase inhibitors (NNRTIs; Nevirapine, Delavirdine, and Efavirenz), the NRTI Abacavir, and the protease inhibitor Amprenavir, are common antiretroviral drugs that cause hypersensitivity, which is rare with other NRTIs or protease inhibitors. Drug hypersensitivity typically manifests as an erythematous, maculopapular, pruritic, and confluent rash with or without fever. The rash is most prominent on the body and arms and usually begins after one to three weeks therapy. Constitutional features (fever, rigors, myalgias, and arthralgias) are often prominent, and can precede the rash (particularly with Abacavir) or occur without rash. Drug hypersensitivity in HIV-1-infected patients is about 100 times more common than in the general population. The pathogenesis of hypersensitivity is unknown[1].

Metabolic features significantly associated with lipodystrophy and protease-inhibitor therapy include hypertriglyceridaemia, hypercholesterolaemia, insulin resistance (raised C-peptide and insulin concentrations) and type 2 (generally non-ketotic) diabetes mellitus. Dyslipidemia at concentrations associated with increased cardiovascular disease occurs in about 70% of patients. These metabolic abnormalities are more profound in those receiving protease inhibitors, and also in those with lipodystrophy[1].

METHODOLOGY

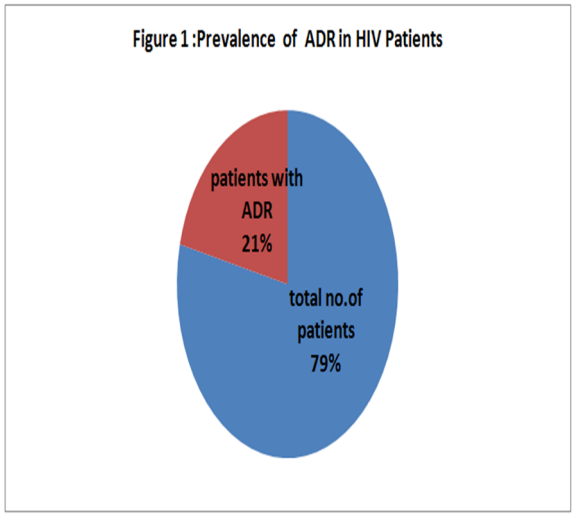
A retrospective study was conducted in the Medical Emergency department of Amrita Institute of Medical Sciences kochi. Out of 203 HIV patients receiving HAART, 60 patients were reported to have ADR's. ADR's were reported and identified by the physicians of emergency department was considered as an ADR. Patients age, sex, MRD no, suspected drug, observed reaction drug changed if any, management of ADR, was collected using Amrita healthcare information system (AHIS) and data collection forms.

RESULTS AND DISCUSSION

Our study included 55 patients reported with ADR's, out of these 23(41.82%) were females and 32(58.18) were males (Figure: 4). As in Table 1, 69% of the patients were in the age group between 41 to 60 following 20% in the age group of 21-40 and the least ADR's (10.91%) were found in the age group between 61-80. In our study 61 suspected ADR'S were observed in 55 patients. As in figure 2, the system which is mostly affected by side effect is hematological system 34(55.73%). Under hematological side effects anemia was more common i.e 25(40.98%) followed by bone marrow suppression 5(8.19%) and pancytopenia 4(6.55%). Dermatological ADR's comes next to hematological side effects 5(8.19%) which include rashes 3(4.91%), discoloration of nails 1(1.63%) and urticaria 1(1.63%). Prevalence of CNS side effects is 4(6.55%). Some of them are as follows: abnormal dreams 3(4.91%), insomnia 1(1.63%), CNS effects 1(1.63%) other most commonly reported ADR's were nausea and vomiting 2(3.27%), dyslipidemia 4(6.55%), lipodystrophy 1(1.63%), hematuria 1(1.63%), peripheral neuropathy 5(8.19%). Hepatic side effects include hyperbilirubinemia 2(3.27%) and increased liver enzymes 2(3.27%).

Table 1: Age distribution of HIV patients with ADR

Age (in years)	Number (out of 55)	Percentage (%)
21 – 40	11	20
41 – 60	38	69.09
61 - 80	6	10.91



Hematological and dermatological systems were most affected by adverse drug reaction and are mainly caused by Zidovudine. Stavudine causes lipodystrophy, peripheral neuropathy and urticaria. Dyslipidemia is caused by Ritonavir. CNS effects such as decreased sleep and abnormal dreams are caused by Efavirenz. While Atazanavir and Efavirenz causes liver function test elevation.

In our study prevalence of ADR was more in male patients compared to female patients. This may be due to difference in body mass index and fat composition, hormonal effects on drug metabolism or genetic constitutional difference in the levels of various enzymes. In a study of Kiran Reddy[3] they found similar high prevalence rate for males. In our study most of the patients belonged to the age group between 41 to 60 so most of the ADR's were found in this age group in our study.

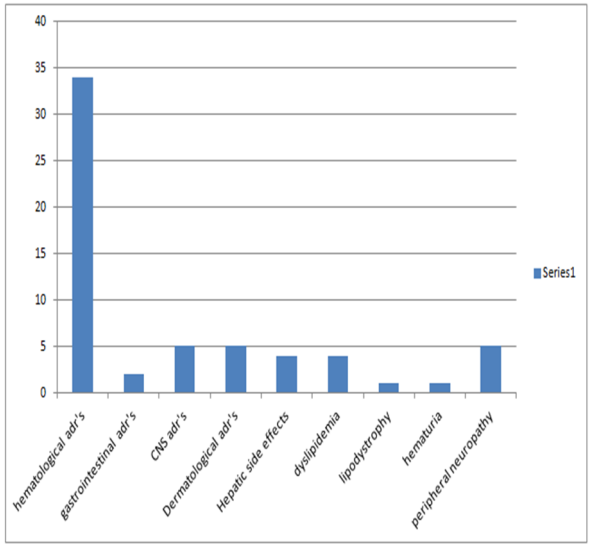


Figure 2: Prevalence of ADR's in HIV patients

It was observed that 21% of the patients experienced ADR during the study period. This incidence rate was less than the study of Jacques Fellay[4], in which 47% of patients presented with clinical and 27% with laboratory

adverse events probably or definitely attributed to antiretroviral treatment. Whereas Kiran Reddy[3] in which 31% of patients experienced ADR's. This variation is because some patients are lost follow up and some only started the therapy recently. Increase in ADR incidence is also due to the side effects of concomitant medications used to treat comorbid illness.

Hematological and dermatological systems are most effected by ADR's (55.73%) which is similar in contrast to the study of AV Kiran Reddy[3] were gastrointestinal system (31.25%) and skin (23.75%) was most predominantly affected organ systems. Similarly, in the study of Khalili[5], gastrointestinal toxicity was most prominent with incidence rate of 63.7% whereas Singh[6] have found skin related toxicity with the incidence rate of 15.83%.

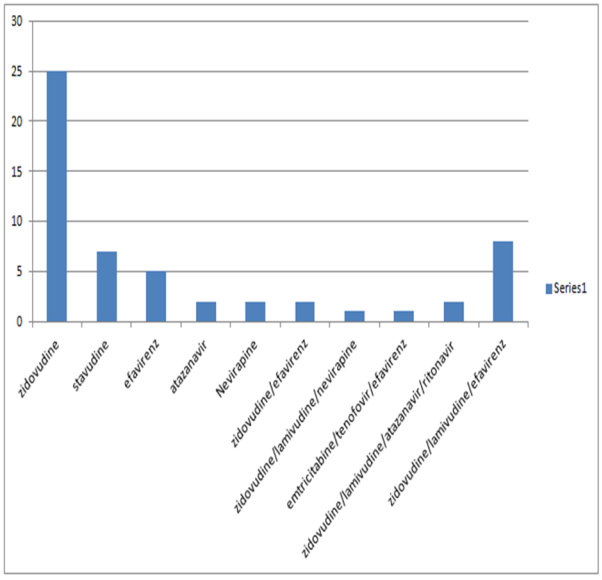
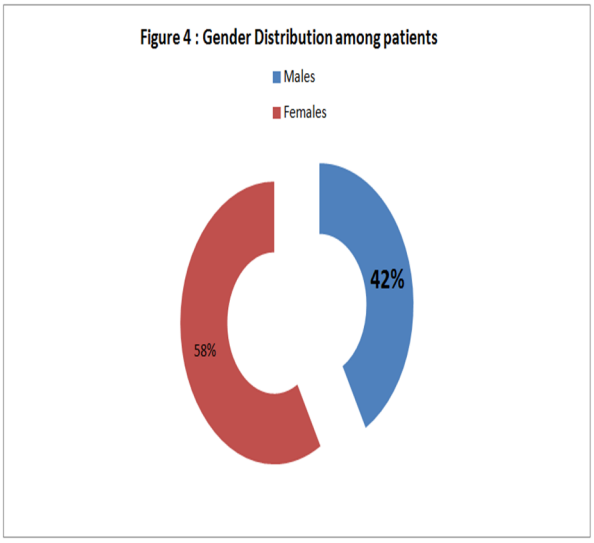


Figure3: Distribution of usage of drugs



We have observed significant relation between Zidovudine and anemia which is also similar to the study of Kiran Reddy[3]. Stavudine causing lipodystrophy, and peripheral neuropathy was also seen in the study of Kiran Reddy[3] and Scarsella[7], Giesen[8]. In contrast we have also observed one case of Stavudine causing urticaria. In contrast to the study results of Fumaz[9] and Subbaraman[10]. We observed Efavirenz induced vivid dreams, cns effects etc. Although 1 case of Efavirenz induced insomnia is seen. Most of the ADR's were seen with Zidovudine (figure: 3) which is contrary to the study of Rajesh[11] where main ADR's observed with Zidovudine and Nevirapine. The main combination therapy used in our study is Zidovudine + Lamivudine + Efavirenz.

CONCLUSION

We have conducted a retrospective study at the emergency department of a tertiary care hospital. In the study the main organ system effected by ADR's are hematological and dermatological systems which was found similar to other referred studies. Zidovudine is significantly associated with induction of anemia. Least ADR's noted were lipodystrophy, hematuria and gastrointestinal ADR's. Zidovudine caused majority of the ADR's. In government settings they only test for the CD4 counts periodically, they are unaware about the side effects of the antiretroviral therapy. Here comes the responsibility or importance of the clinical pharmacist in investigating such ADR's and plays an efficient role in increasing the quality of life. Therapeutic Drug Monitoring and awareness of adverse effects will help to reduce the toxicities and also the development of improved second-generation and third generation antiretroviral compounds.

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