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Research Article

ASSESSMENT OF ADVERSE DRUG REACTIONS DUE TO ANTIRETROVIRAL DRUGS: A RETROSPECTIVE OBSERVATIONAL STUDY

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A R T I C L E I N F O

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A B S T R A C T

Antiretroviral therapy (ART) has been proved to be efficacious in reducing morbidity and mortality related to Human Immunodeficiency Virus (HIV) infection. However it is also associated with long and short term adverse drug reactions (ADRs) which lead to non-adherence to ART and is one of major causes of hospitalization and higher cost of treatment. The present study focuses on ART induced ADRs by spontaneous reporting system under Pharmacovigilance Program of India. Suspected adverse drug reaction reporting forms provided by PvPI were used to collect the data from ART centre of Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai. A total of 94 spontaneous ADR reports were collected from December 2015 to December 2019. Among 94 reports, 116 ADRs were analysed and found that majority of the reactions were blood & lymphatic system disorders (anaemia n=53). Among all the reports, the majority were in females (n=59) and maximum number of ADRs were in the age group of 31-59 yrs (n=80). The most implicated fixed dose combination of ART was found to be Zidovudine+Lamivudine+Nevirapine (n=66) and on causality assessment 72 were found to be "Probable "category. Our study concludes that the majority of the ADRs were "anaemia" due to ZLN regimen. The success of ART depends on the patient adherence and one of the most common reasons for poor compliance is occurrence of ADRs. Early detection and prevention of ADRs is the key function of treating physician to optimize adherence and to maintain safety and efficacy of antiretroviral therapy.

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a major global health problem. According to the United Nations Programme on HIV and AIDS (UNAIDS) report, 36.7 million people were living with HIV at the end of 2018 and 24.5 million were accessing antiretroviral therapy (June 2019) worldwide[1,2]. HIV prevalence (in 15–49 years adults) in India was estimated to be 0.22% as per "India HIV estimation 2017 report". The total number of people living with HIV (PLHIV) in India is estimated at 21.40 lakhs in 2017. Children (< 15 years) account for 0.61lakh while females (15+years) accounts for 8.79 lakh PLHIV in India[3].

The Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection, Recommendations for a Public Health Approach, were published by the World Health Organization (WHO) in 2016. These guidelines outline a detailed schema for diagnosis, treatment of HIV, and the related opportunistic infections, monitoring response to treatment, dealing with antiretroviral drug toxicities and substitutions, managing co-morbidities, HIV prevention including pre and post exposure prophylaxis, switch of antiretroviral regimen and the general care of the HIV positive individuals[4].

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). The Government of India, Ministry of Health and Family Welfare, provides this combination chemotherapy to the people infected with HIV. The easy availability and use of antiretroviral therapy from government setup, dramatically reduces the disease related morbidity as well as increases the quality and life - span of the patients. These therapies have a greater impact on reducing HIV viral load and provide durable suppression of viral replication[5,6].

However, antiretroviral drugs are associated with a broad range of adverse effects which lead to poor patient adherence and frequent treatment modifications. These adverse events may be acute or chronic, mild or serious affecting individual patients and has a serious impact on public health. Most of the adverse drug reactions remain unnoticed or not reported by the patients. Thus, continuous monitoring of ART will help to achieve the ultimate goal of safe and effective therapy[6].

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Aim and Objectives

To assess the adverse drug reactions due to antiretroviral drugs prescribed in HIV infected patients by spontaneous ADR reporting system.

MATERIALS AND METHODS

A retrospective observational study was conducted in an outpatient department of ART centre of Madras Medical College (MMC) & Rajiv Gandhi Govt. General Hospital (RGGGH), Chennai from December 2015 to December 2019 using suspected adverse drug reaction (sADR) reporting form provided by Pharmacovigilance Program of India (PvPI). All the spontaneous adverse drug reactions reported to fixed dose combination of ART were included in the study. ADRs due to the medications used for treating the opportunistic infections and co-morbid conditions were excluded. Patient demographic details, FDC and ADR related information was collected from the patient case records and were filled in the sADR reporting form.

All the sADR reporting forms were analyzed for the patient age group, gender, seriousness of the ADR, fixed dose combination of ART implicating ADR(s) and the causality assessment (WHO-UMC scale). Further, all the ADRs observed were grouped on the basis of system organ class which they affected.

RESULTS

A total of 116 ADRs were analysed from a total of 94 reports. Out of 94 reports, 34 belonged to males followed by 59 females and 1 transgender (Fig 1).

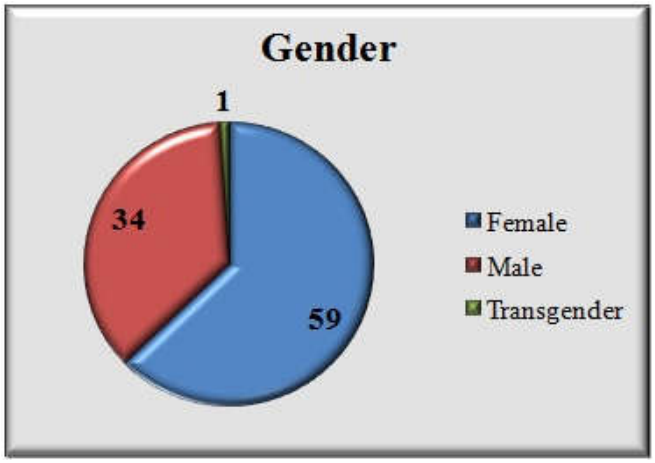

Fig 1 Gender wise distribution of ADR reports

The age group in which maximum number of ADRs manifested are middle aged adults (31-59 yrs of age) (n=80) followed by young adults (19-30 yrs of age) (n=9), children (≤18 yrs of age) (n=3) and elderly (≥60 yrs of age) (n=2) (Fig 2).

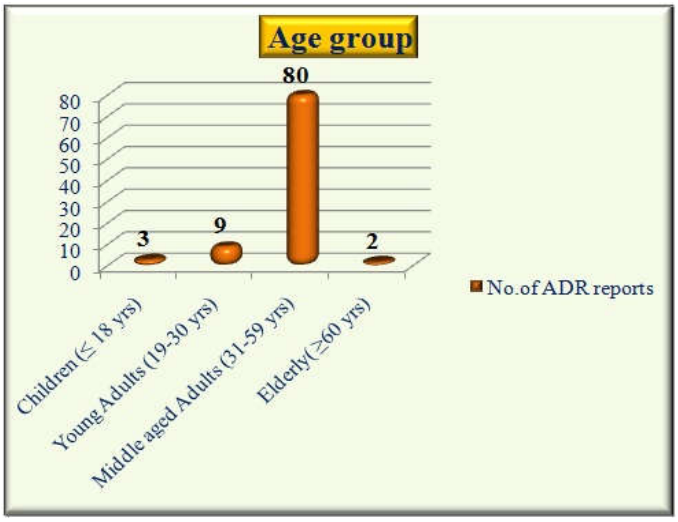

Fig 2 ADRs occurred in the Age group

The most implicated ADRs are grouped into System Organ Class (SOC) and the most predominant ADRs belonged to Blood & Lymphatic system disorders (Anaemia, n=53) followed by Skin and Subcutaneous tissue disorders (Skin rash n=7, Itching n=3, Pallor n=3, Stevens Johnson Syndrome n=2, Blisters n=1 and Exfoliative lesions n=1), Nervous system disorders (Giddiness n=9, Neuropsychiatric disturbances n=1), Gastrointestinal disorders (Vomiting n=4, Diarrhoea n=3, throat pain n=1), Renal and Urinary disorders (Renal failure n=6), Metabolic & Nutrition disorders (Lipodystrophy n=6), Investigations (abnormal Liver Function Tests (LFTs) n=6), General disorders (Pedal oedema n=2, Fatigue n=2, Fever n=1, Puffiness n=1) and Respiratory disorder(dyspnoea n=4) (Table 1).

Table 1 ADRs grouped according to System Organ Class (SOC)

S.no	Adrs-soc	No. Of adrs
1	Blood & Lymphatic system disorders	Anaemia (53)
2	Nervous system disorders	Giddiness (09) Neuropsychiatric disturbances (01)
3	Skin & Subcutaneous tissue disorders	Rash (07) SJS (02) Itching (03) Exfoliative lesions (01) Blisters (01) Pallor (03)
4	Investigations	Abnormal Liver Function Tests (06)
5	Renal & Urinary disorders	Renal failure (06)
6	Metabolism & Nutrition disorders	Lipodystrophy (06)
7	Gatrointestinal disorders	Vomiting (04) Diarrhoea (03) Throat pain (01)
8	Respiratory & Thoracic disorders	Dyspnoea (04)
9	General disorders	Pedal oedema (02) Puffiness(01) Fatigue (02) Fever (01)

It was found that the most implicated ART-FDC regimen was Zidovudine+Lamivudine+Nevirapine (ZLN) (n=66) followed by Tenofovir+Lamivudine+Efavirenz (TLE) (n=28**) (Fig 3)**

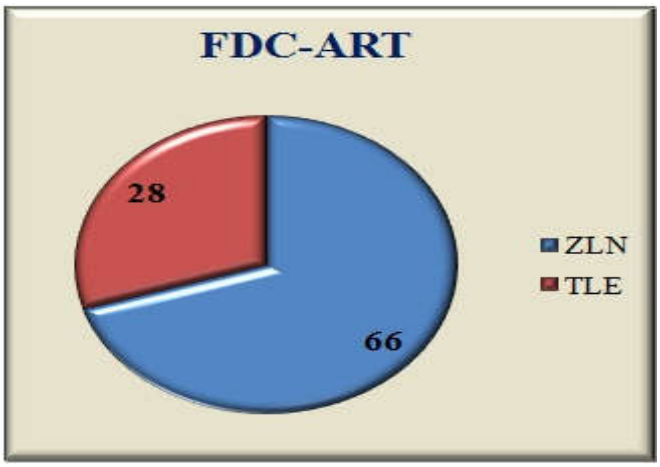

Fig 3 FDC of ART implicating ADRs

It was found that the most implicated ADRs with ZLN regimen were Anemia (n=51), followed by lipodystrophy (n=6) and abnormal LFTs (n=5). Similarly the most implicated ADRs with TLE regimen were giddiness (n=9) followed by skin rash (n=7), renal failure (n=5) and SJS (n=2).

Among 94 reports, 91 reports are categorized into "serious" as per ICH E2A guidelines, of which maximum number of ADRs are falling under "other medically important" category (n=68) (Table 2).

Table 2 Seriousness of the reaction

S.No.	Seriousness Criteria	No. of reports
1	Death	0
2	Life threatening	0
3	Hospitalization/Prolonged	23
4	Congenital anomaly	0
5	Disability	0
6	Other medically important	68
	Non serious	03

The causality assessment was done using the WHO-UMC causality assessment scale and was found that 72 reports were under "Probable" and 22 were under "Possible" category (Fig 4).

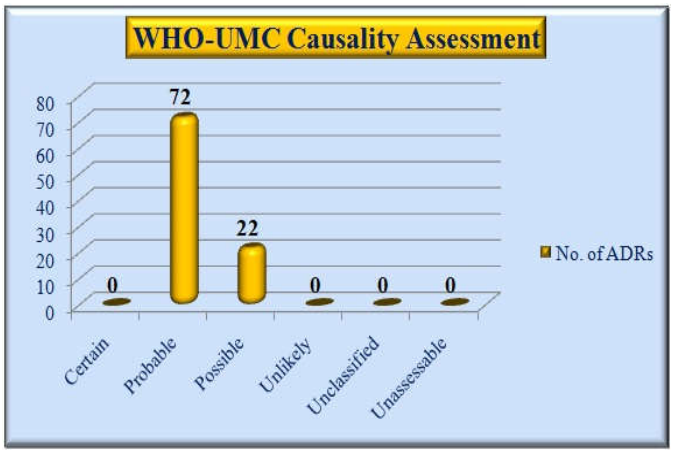

Fig 4 WHO-UMC causality assessment of ADR reports

DISCUSSION

In this study it was found that the predominance of ADRs was in Females than males and similar findings were shown in earlier study by *Rentia V et al*[7] and *Raikar et al*[8] but is in contrast to other studies *Mukta et al*[4], *Rajesh R et al*[9] and *Kumar et al*[10].

The Prevalence of ADRs due to ART in this study was more in the age group of 31–59 years which is in concordance to previous studies conducted by *Raikar et al*[8] but contrast to *Rita et al*[5].

Based on the WHO-UMC causality assessment scale, most of the reports were under "Probable followed by "possible" category and is contrast to *Rakshit S et al*[6] and is similar to *Raikar et al*[8] *and Rajesh R et al*[9].

In our study the most common systems affected by ADRs of ART were Blood & Lymphatic system disorders followed by Skin and subcutaneous tissue disorders and is in contrast to study of, *Takaki et al*[12] and *Ramanjireddy et al*[13].

Study of *Bandyopadhyay, et a1*[11] and *Ramanjireddy et al*[13] showed TLE regimen was most offending FDC causing ARDs while the present study showed most offending FDC causing the ADRs was ZLN regimen.

CONCLUSION

Though antiretroviral drugs are the mainstay of the treatment for HIV/AIDS, the success of ART depends on the treatment adherence, and one of the most common reasons for poor compliance is occurrence of ADRs. To optimize adherence and to maintain safety and efficacy of antiretroviral therapy, the treating physicians must focus on early detection and prevention of ADRs. The present study found that the ADRs are more common in females than males and the most implicated ADR was Anaemia with ZLN regimen. Further studies need to be carried to find out the other factors that may implicit the ADRs. The finding of this study showed that there is a need for intensive monitoring for ADRs in HIV positive patients in India.

Limitations

There are several limitations to this study. This was a retrospective observational study based on the spontaneous ADR reporting system only. So, we could not quantify the risk factors associated with the safety of ART regimens. There is also the strong possibility of under-reporting.

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Disclaimer

The data was collected from ART center of Madras Medical College & RGGGH and same was uploaded in VIGIFLOW. The likelihood that the suspected reaction is drug related is not same in all cases in this study. The views are expressed by the authors of this study and does not represent the opinion of NCC-PvPI or its scientific committee of other regulatory agencies.

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