ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 02 | February - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A PROSPECTIVE OBSERVATIONAL STUDY TO EVALUATE THE ADVERSE DRUG REACTIONS ASSOCIATED WITH ANTI-RETROVIRAL THERAPY AT TERTIARY CARE HOSPITAL, GOVERNMENT GENERAL HOSPITAL, ANANTAPURAMU.

Pharmacology

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ABSTRACT

Background : The cornerstone of the treatment of HIV-AIDS patients is the Anti-Retroviral Therapy; which changed the life-threatening disease to a chronic disease. ART is effective in decreasing the morbidity and mortality; it is associated with adverse drug reactions. The ADRs tend to decrease the patient adherence and sometimes the overall benefit of the ART. **Methodology:** A total of 142 patients were included in the study. Written informed consent and Institutional ethical committee approval obtained prior to the study. The patients were monitored for ADRs and the assessment of causality, severity and preventability was done by WHO-UMC scale, Modified Hartwig & Seigel scale and Modified Schumock & Thornton scales respectively. **Results:** A total of 188 ADRs were noted. As per WHO scale, 160 ADRs were probable and 28 were possible. Based on the severity assessment, 20 ADRs were mild, 160 ADRs were moderate and 8 ADRs were severe in nature. Among the reported ADRs, 140 were definitely preventable and 24 were probably preventable. Antiretroviral drugs responsible for ADRs were Zidovudine (92), Stavudine (42), Nevirapine (20), Effavirenz (20), Lamivudine(10), Tenofovir (2), and Ritonavir (2). Among the reported ADRs, major ADRs were Anemia (50), Skin rashes (20), Hepatitis (20), Vomiting (20), Lactic acidosis (18), IRIS (10). **Conclusion:** Regular monitoring of the HIV patients on ART is essential to identify and resolve ADR related morbidities.

KEYWORDS

Anti-retroviral Therapy, ART, AIDS, HIV

INTRODUCTION

The Human Immunodeficiency Virus (HIV) has changed from life threatening to chronic condition due to the almost universal use and accessibility of antiretroviral therapy (ART) among HIV patients (Hawkins, 2010).As with any chronic therapy, drug related toxicities remain a major challenge in resource-limited settings due to limited formulary and inadequately trained personnel (Murphy RA, 2007).Adverse drug reactions (ADRs) can often cause significant morbidity among individuals on antiretroviral therapy (ART), occasionally leading to mortality. Treatment limiting drug toxicities can affect the patient adherence to treatment, clinical outcomes and cost to the public health system. (Ciconi P, 2010)

Antiretroviral (ART) therapy works by providing suppression of viral load and restoring the immune system. It is estimated that out of the 38 million people living with HIV worldwide, 25.4 million were receiving ART in 2019 (htt).Nearly, 6.6 million HIV/AIDS related deaths worldwide have been prevented as a result of ART. Despite these gains, adverse reactions to these medicines decrease effectiveness of the ART programmes. (Mehta, 2011) (Organization, 2006)

The risk of ADRs arises because of the effect of the disease on the immune systems and the safety profiles of the complex ART drugs (Mehta, 2011). There are a number of ADRs related to ART that have been documented, and may be mild to severe; and short to long term depending on the environment (Reddenna L, 2013) (Nemura T, 2013) .ADRs in developing countries may differ from those in developed countries because of high prevalence of conditions such as malnutrition, tuberculosis and patients presenting with advanced HIV disease (Subbaraman R, 2007). Short term ADRs are a potential threat to successful initiation and adherence to ART (Max B, 2000). ADRs may be common or specific to class of drugs. Drugs classified as non-nucleoside reverse transcriptase inhibitors (NNRTIs) are known to cause rashes and hepatotoxicity. On the other hand drugs classified as nucleoside reverse transcriptase inhibitors (NRTIs) are known to cause anemia, nausea, rashes, lipoatrophy and lactic acidosis (Hawkins, 2010).

Apart from ADR depending on the environment and the type of ART regimen, a number of other risk factors have been identified, that include age, gender, duration on treatment, disease biomarkers such as CD4 count and viral load and body mass index (BMI) (Eluwa GI, 2012). These risk factors have been found to interact with type of ADR. The longer a patient is on ART the less likely they would experience ADRs; possibly as a result of stability in ART regimen, coming after many changes and eventually settling on an acceptable regimen.

The purpose of this study was to evaluate causality, severity and preventability of known ADRs among HIV positive patients on ART.

METHODOLOGY

The present study was a prospective observational study conducted at Government General Hospital, department of DVL, Anantapur from JAN 2019 – DEC 2020.

A total of 150 patients were included in the study, out of which 8 patients lost to follow up. Written informed consent from every participating individual was obtained prior to the study. Ethics committee approval was obtained from the Institutional Ethical Committee prior to the study.

All the in – patients receiving ART were monitored during the study period for suspected ADRs. WHO causality assessment scale, Modified Hartwig & Seigel scale and Modified Schumock & Thornton scales were applied to assess the causality, severity and preventability of the reported ADRs respectively. The collected data was analyzed appropriately using SPSS software.

RESULTS

Demographic Details of study population

Demographics	No. Of patients	Percentage (N=142)
Male	74	52%
Female	68	48%
Age (Years)		
1-18	8	5.6%
18-30	32	22.4%
30-50	88	62%
>50	14	10%

Majority of the study individuals were of the age group of 30-50.

WHO Causality assessment

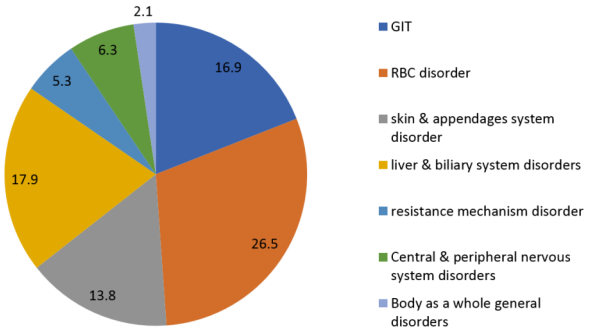
Category	No. of ADRS	Percentage (N=188ADRS)
Probable	160	85%
Possible	28	15%

Out of the total ADRs, 85% had probable causal association with the study drugs.

Severity Assessment

Levels	No. of ADRS	Percentage (N=188ADRS)
Mild		
Level 1	6	3.2%
Level 2	14	7.4%
Moderate		
Level 3	92	49%
Level 4(a)	40	21.2%
Level 4(b)	28	15%
Severe		
Level 5,6,7	8	4.2%

85.2% of ADRs fall into moderate severity category.



Percentage Of System Wise Adverse Drug Reactions Associated With Anti-Retroviral Therapy

Suspected Drugs invoved in ADRs with the Organ System Affected

WHO ART system organ class (soc code) ADRs	Drug(s) suspected ADRs	Number of ADRs and %(n=188)
1. Gastro-intestinasystem disorders(0600)		
Vomiting	AZT, d4t	20(10.6%)
Nausea	AZT	6(3.2%)
Diarrhea	3TC	4(2.1%)
Pancreatitis (Alkaline Phosphatase)	AZT	2(1%)
2. RBC disorders (1210)		
Anemia (Hemogram)	AZT	50(26.5%)
3.skin &appendages system disorder (0100)		
Rash (AEC count)	NVP, EFV	20(10.6%)
Pigmentation of nails	AZT	6(3.2%)
4. Liver and Biliary system disorders (0700)		
Hepatitis (L F T)	NVP, EFV	20(10.6%)
Lipodystrophy	d4T	8(4.2%)
Gynecomastia	RTV, EFV	4(2.1%)
Diabetes (Blood Sugar)	d4T	2(1%)
5.Resistance mechanism disorders (1830)		
IRIS	AZT+3TC+NVP, D4T+3TC+NVP, TDF+3TC+NVP	10(5.3%)
Central & peripheral nervous system disorders (0410)		
Peripheral neuropathy	d4T	8(4.2%)
Giddiness	EFV	4(2.1%)
Body as a whole general disorders (1810)		
Headache	3tc	4(2.1%)

Anemia had higher incidence of about 26.5% , followed by vomiting, rash and hepatitis.

DISCUSSION

The ADRs impose a psychological and socioeconomic burden not only on HIV positive patients but also on public health sector making monitoring ADRs to ART a necessity. Studies on the incidence of ADR from developing and developed countries have reported incidence of ADR among patients on ART to range between 11%-35.9% (Patrice S, 2010) with incidence as high as 54% in the presence of opportunistic infection.

The long term effects of ARTs include peripheral neuropathy and lipodystrophy associated with stavudine (Palella FJ Jr, 1998) anaemia associated with zidovudine (Laurent C, 2008) and nevirapine based hepatotoxicity and rash. (Phanuphak N, 2007) Incidence of hepatotoxicity was observed to be 16% and 8% for patients on NVP and EFV respectively (Sulkowski MS, 2003) while incidence of anaemia ranged from 3- 12% among patients on zidovudine in developing countries.

There is sufficient evidence that links treatment success to adherence to ART. However adverse drug reactions affect the adherence to treatment. (Duval X, 2004) It is thus imperative that clinicians clearly understand ADRs, readily recognize them in patients and manage them effectively.

The likelihood of developing an adverse drug reaction was highest in the first six months of commencing antiretroviral therapy. Xavier et al. (Duval X, 2004) proffered an explanation that early occurrence of ADRs is an expression of a mechanism of intrinsic intolerance rather than of a time-dependent toxic accumulation process.

Close monitoring of patients within this time frame is thus imperative to prevent the occurrence of severe ADRs, improve adherence as well as improve documentation of ADRs. However 45% of the reported ADRs occurred within 12-24 months of commencing ART. This calls for the need to intensify long term ADR monitoring in patients on ART. Some studies have proposed time-dependent toxic accumulation as the mechanism of developing an ADR long after commencing medication. Thus monitoring for ADR should be an ongoing process as we have both early onset and late onset ADRs.

Adding a laboratory component to the ADR screening would go a long way in determining biochemical markers that would help to improve patient management. Having sound knowledge of the risk factors or common ADRs associated with different ART regimen can help focus scarce resources to managing ADRs in these settings.

Summary & Conclusion

Adverse drug reactions remains a reality in ART administration for HIV care, detailed counselling during the early stage of ART initiation, along with good clinical and laboratory monitoring, can go a long way in maintaining the durability of first-line regimens in resource-limited settings. The high incidence of drug-induced anemia in population should be urgently addressed with alternative first-line agents, or close laboratory monitoring. High treatment efficacy despite decreased drug safety may be seen among patients with limited options; nevertheless patients deserve superior ART regimens that curtail the risk of severe life-threatening toxicities.

It has highlighted the importance of optimal drug selection and monitoring of vulnerable patients in mitigating the clinical severity of the adverse reactions. Further analyses using much larger and more complete data from different settings would be needed to solidify the findings in this study.

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