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Original Article

Anti-retroviral therapy (ART) regimens and associated adverse events: A prospective observational study in a Tertiary Care Hospital of South Odisha

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ABSTRACT

Background: *HIV prevalence in Odisha has reduced to 0.13% from 0.31 % (2010) since the advent of antiretroviral therapy (ART). It has been proven to be efficacious and also lifesaving in patients living with HIV (PLHIV). However their associated adverse events [AEs] are a matter of serious concern. Therefore the present study was conducted to evaluate the AEs following various ART regimens.*

Methods: *This was a prospective observational study (September 2018 - August 2019) among PLHIV and receiving ART from the outpatient setting of ART centre of M.K.C.G. Medical College & Hospital, Berhampur, Odisha. Data were collected and analyzed to find out the demographic characteristics, causality and severity of adverse events (AEs) with different ART regimens.*

Results: *The study showed that, 317 patients were identified to be suffering from one or more adverse events. Female gender, 40-49 years age group were more prone to adverse events. Among them, Eight (8) cases were labeled as 'serious' category and were hospitalized. 97.5% patients were graded as 'possible' [WHO-UMC causality assessment scale]. Patients were administered 10 types of ART regimen of which most AEs (217) were observed with Tenofovir + Lamivudine + Efavirenz (TLE). Most commonly observed adverse events were acid peptic disease (89), myalgia (85), acute respiratory tract infection (18), anemia (15), neuritis (15).*

Conclusion: *ART regimen has considerably reduced the morbidity and mortality of PLHIV, but increased numbers of AEs, demands intensive monitoring and timely intervention for tackling the associated AEs to improve patient compliance and quality of life.*

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INTRODUCTION

In 2017, the percentage of people living with HIV and tuberculosis who were being treated for both diseases was 33.4%, which was 36.3% in 2015. Of the 2 100 000 adults living with HIV, 880 000 (41.9%) were women. HIV treatment was also accordingly higher among women than men, with 63% of adult women living with HIV on treatment, compared to 50% of adult men. In India in 2017, 2 100 000 people were living with HIV. [1]

According to the, 'India HIV Estimation 2017 report', HIV prevalence in India is estimated to be 0.22% (0.16% – 0.30%). As per the same report, adult HIV prevalence is estimated at 0.25 %(0.18-0.34) among males and at 0.19% (0.14-0.25) among females. The adult HIV prevalence at national level has showed a steady decline from 0.38% in 2001-03 through 0.34% in 2007, 0.28% in 2012 and 0.26% in 2015 to 0.22% in 2017. The total number of people living with HIV (PLHIV) in India is estimated at 21.40 lakhs (15.90 lakhs–28.39 lakhs) in 2017. [2]

Success of any ART Program depends on patient adherence to the prescribed regimen and major factor for non-adherence has been drugs toxicity. Studies related to HIV/AIDS indicate that high levels of adherence are necessary for prevention of drug resistance, viral suppression, and disease progression. [3]

Antiretroviral therapy (ART) has been proven to be efficacious and also lifesaving in patients living with HIV (PLHIV). Adverse effects have been reported with more or less all anti-retroviral drugs and need measures to overcome. At times they are life threatening leading to non-adherence, substitution / switching off or discontinuation of therapy. Therefore ART associated adverse events [AEs] are a matter of serious concern. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) like Efavirenz (EFZ) and Nevirapine (NVP) are known to cause rashes and hepatotoxicity. Another class of antiretroviral drugs named Nucleoside reverse transcriptase inhibitors (NRTIs) like Zidovudine (AZT) and

Stavudine (d4T) are known to cause anemia, nausea, rashes, lipoatrophy and lactic acidosis. [4]

A number of ADRs related to ART that have been documented, which vary from a mild to severe degree; and short to long term depending on the environment. Among the different risk factors, high prevalence of malnutrition, tuberculosis, advanced HIV disease etc. expose people residing in developing countries to more ADRs than from those belonging to developed countries. [5] One of our studies conducted in the same ART Centre where the present study was done showed a 8.92% drug related toxicity among patients on regular ART treatment.[6]

The timing of ADRs may also depend on the type of drugs. Studies have shown that patients on Efavirenz, Lamivudine and Zidivudine or Indinavir, Zidovudine and Lamivudine may present with ADRs within the first 12 or 24 weeks, respectively.[7,8]

Apart from ADR depending on the environment and the type of ART regimen, other risk factors that have been identified, include patient age, gender, duration on treatment, disease biomarkers such as CD4 count and viral load and body mass index (BMI). A complex association exists between these risk factors and the type of ADR. For instance females are more likely to develop rashes and hepatotoxicity. Patients aged more than 40 years are at a higher risk of developing peripheral neuropathy. [9-11]

Adverse effects often trivial are the major cause of patient drop out at the ART centres. Most of the adverse drug reactions remain unnoticed or not reported by the patients. Thus, careful and continuous evaluation will be of benefit to achieve ultimate goal of making the ART treatment more safe and effective to the patients. [12] Therefore, this study was conducted for early recognition of drug regimen associated adverse reactions and assessment of their causality, severity and preventability. Thus the ultimate goal was early modification of drug regimen to improve patient's compliance and tolerability to the therapy and reduction of morbidity and early mortality.

METHODS

STUDY DESIGN

The present study was conducted in an outpatient setting of Nodal ART centre of Maharaja Krushna Chandra Gajapati Medical College & Hospital, Berhampur, Odisha. The ethical approval was obtained from Institutional Ethics Committee before the initiation of study. Following necessary approvals, from the nodal centre, data was collected from the patients on ART regimen during the study period. A written informed consent was taken from the patients after explaining the study procedure.

It was a prospective observational study for a period of one year (September 2018 - August 2019) among patients living with HIV and receiving antiretroviral therapy. A total of 3000 patients enrolled randomly for the study, from which 317 cases of ADRs were observed during the study period. These patients were intensively monitored for any adverse clinical events during follow - up visits to the ART Centre. Subjects of either sex, aged 0-80 years, receiving ART during Sep-2018 to Aug-2019 were included in the study. While the patients with any other co-morbidity like diabetes mellitus, hypertension, chronic kidney disease and pregnant women were excluded from the study. Diagnosis of adverse events was made on the basis of patient's complaints and/or from the patient's attendants, their morphological changes during routine clinical examinations as well as a review of outpatient case records, laboratory reports, clinician's notes and prescriptions at each follow – up visit. All the information was recorded in the 'Suspected ADRs reporting form' designed by Indian Pharmacopoeia Commission, Ghaziabad, India. Any other details regarding drug therapy and associated adverse events was obtained from the treating physician. The World Health Organization (WHO) ADR probability scale and Naranjo algorithm were used for causality assessment.

RESULTS

In this study, among 317 patients who developed ADRs, 152 (48%) were males, 160 (50%) were females and 5 (2%) belonged to transgender category. (Fig.-1). Most of the patients were between the age group of 40- 49 years (35.65%) followed by 30- 39 years (31.86%) (Fig.-2).

Among all the ADRs most common ADR was Acid peptic disease (89, 28.08%) followed by myalgia (85, 26.81%), acute respiratory tract infection (18, 5.68%), anemia (15, 4.73%), neuritis (15, 4.73 %), hepatitis (13, 4.10 %), dizziness (11, 3.47%) peripheral neuropathy and fever (9, 2.84%). Other adverse drug reactions very rare are depicted in Table -1 and 2.

In our study, most of the ADRs observed with TLE regimen (Tenofovir + Lamivudine + Efavirenz) (68.45%) followed by ZLN regimen (Zidovudine + Lamivudine + Nevrapine)) (20.19%), TLAR regimen (Tenofovir + Lamivudine + Atazanavir + Ritonavir) (4.73 %), TLN regimen (Tenofovir + Lamivudine + Nevirapine) (2.84%) The percentage of associated ADRs with various types of ART regimen is shown in Fig- 3.

Causality assessment was done by WHO causality assessment scale, where 309 patients presented with ADRs were possible (97.48%) and 8 patients were unlikely (2.52%). (Fig. - 4)

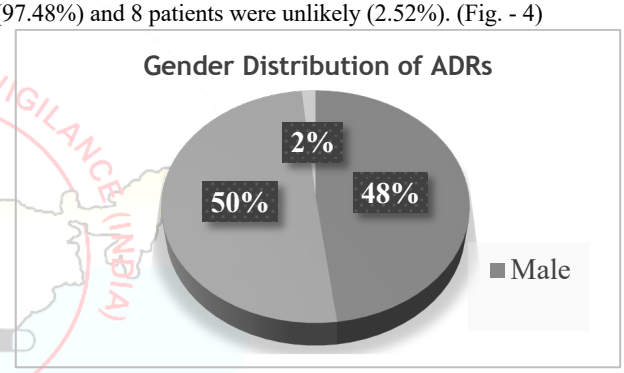

Fig: 1 Gender Distribution of ADRs

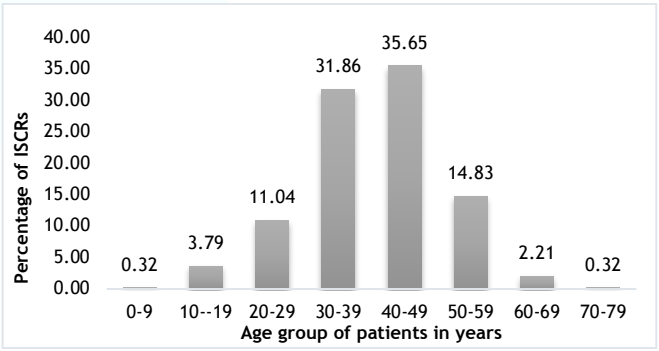

Fig: 2 - Age Distribution of ADRs

Table 1. Distribution of ADRs based on Type of ART Regimen

Adverse drug reactions	Types of ART regimen									
	TLE	ZLN	TLN	TLAR	ZLAR	ZLL	ZLE	ALE	AbTLAR	TLR
Acid peptic disease	64	15	5	3	1			0		1
Acute Deafness	1	0	0	0				0		
Acute Respiratory Tract Infection	12	3	0	1				2		
Anaemia	4	9	1	0			1	0		
Arthritis	3	0	0	0						

Cervical cancer	1	0	0	0					
Chronic hepatitis	2	2	0	0					
Diarrhoea	2	0	0	0					
Dizziness	10	0	0	0	1				
Fever	7	2	0	0					
Gastritis	2	0	0	0					
Gynaecomastia	3	0	0	0					
Hepatitis	0	0	1	2					
Hepatitis B surface antigen positive	9	3	0	1					
Herpes labialis	1	0	0	0					
Hypersensitivity reaction	0	0	0	0					1
Immune reconstitution inflammatory syndrome	3	0	0	0				1	
Insomnia	4	0	0	0					
Jaundice	1	0	0	0					
Myalgia	53	26	1	2	1		1	1	
Neuralgia	1	0	0	1					
Neuritis	12	1	0	2					
Peripheral nephropathy	9	0	0	0					
Pruritus	5	1	0	2					
Psychosis	1	0	0	0					
Nephrotic syndrome	0	0	0	0		1			
Neuropathy	0	1	0	0					
Oral candidiasis	1	0	0	0					
Pyelo nephritis	1	0	0	0					
Rash	3	0	1	1					
SJS	1	0	0	0					
Tinea cruris	1	0	0	0					
Tongue ulcer	0	1	0	0					

Table 2: Distribution of types of ADRs among total ADRs reported.

Sl. No.	Types of ADR	Percentage of ADR
1	Acid peptic disease	28.08
2	Acute Deafness	0.32
3	Acute Respiratory Tract Infection	5.68
4	Anaemia	4.73
5	Arthritis	0.95
6	Cervical cancer	0.32
7	chronic hepatitis	1.26
8	Diarrhoea	0.63
9	Dizziness	3.47
10	fever	2.84
11	gastritis	0.63
12	Gynaecomastia	0.95
13	hepatitis	0.95
14	Hepatitis B surface antigen positive	4.10
15	Herpes labialis	0.32
16	hypersensitivity reaction	0.32
17	Immune reconstitution inflammatory syndrome	1.26
18	insomnia	1.26
19	jaundice	0.32
20	myalgia	26.81
21	neuralgia	0.63
22	neuritis	4.73
23	peripheral nephropathy	2.84
24	pruritus	2.52
25	psychosis	0.32
26	nephrotic syndrome	0.32
27	neuropathy	0.32
28	oral candidiasis	0.32
29	pyelo nephritis	0.32
30	rash	1.58
31	SJS	0.32
32	tinea cruris	0.32
33	tongue ulcer	0.32

(T: Tenofovir, L: Lamivudine, E:Efavirenz, Z: Zidovudine, N: Nevirapine, A: Atazanavir, Ab:Abacavir, R: Ritonavir)

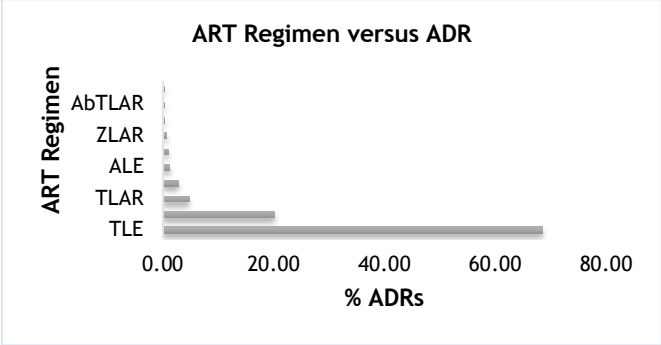

Fig 3: Percentage of Cases associated with ART regimen

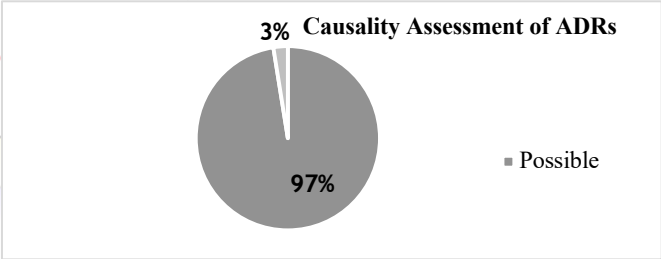

Fig. - 4: Causality Assessment of ADRs

DISCUSSION

This study explored the adverse drug reaction patterns associated with different combination regimens of antiretroviral therapy. Poor adherence and development of resistance to the therapy can be detected by evaluating the ADR pattern. Age, gender, type of ARV drug regimens, period of initiation of ART was found to be associated with HIV/AIDS drug related adverse reactions.

In this study, about 81.42% patients presented with ADRs. The study also found higher prevalence of ADR in females (50%) than males (48%). Similar findings were reported by *Praveen Kumar et al* that females (60.55%) had higher prevalence of ADRs than males (39.45%).[13] In contrast to *Anshu Kumar Jha et al*, a higher prevalence in males (53.5%) compared to females (46.5%).[14]Our study reported that most of the patients were between the age group of 40- 49 years (35.65%) followed by 30- 39 years (31.86%). On the contrary, *Eluwa et al* reported that age and gender were not significantly associated with ADRs. [15] These variations may be due to study design, sample size, or demographic variations, hormonal effects, immunological status, drug susceptibility, drug metabolism and elimination, or genetic constitutional differences on the levels of various enzymes as reported by *Patel N M et al*. [16]

Gastrointestinal, neurological, haematological and dermatological adverse drug reactions were commonly observed in this study. Majority of ADRs were reported by TLE and ZLN based regimens. In our study, anaemia (15, 4.73%) reported and most of them were associated with Zidovudine based regimens. A study by *Kenneth et al* reported 4.3% cases of anaemia of which 94.5% were reported in

patients who received Zidovudine - based regimens. [17] Similar results were found by *Bhuvana et al*, where anaemia (55.06%) was seen with Zidovudine. [18] This might be resulting from bone marrow suppression action of Zidovudine that leads to anaemia and thrombocytopenia.

Different types of cutaneous hypersensitivity reactions were reported in patients receiving antiretroviral therapy and most common cause of treatment interruption in our study. One case of severe exfoliated blistering rashes of Steven Johnson Syndrome with TLE regimen was reported. Efavirenz was also found to be associated with other skin rashes, pigmentations and raised liver enzymes. Efavirenz associated of Steven Johnson syndrome was also reported by *Ward H et al*. [19] Efavirenz use was observed as a risk factor for peripheral neuropathy, insomnia, giddiness and other central nervous system problem. Thus, early detection, withdrawal of suspected drugs, identification of causative agents and appropriate treatment of associated adverse events are essential for the prevention of additional exposure as well as disease progression.

Due to high rates of ZLN regimen associated ADRs from a number of the past study reports, [20-22] presently HIV patients are prescribed Tenofovir (TDF) containing regimen as a first line ARV treatment. Contrary to the above studies, the present study found that TLE regimen has been associated with higher ADR rates. Similar results were found by Lieketseng *et al,* where Tenofovir (TDF) containing regimen was used as a first line ARV treatment in the study as other regimens (ZLN/ZLE) had high rates of ADRs. [23] Therefore careful monitoring and further studies comparing ADRs among patients on TDF containing regimen with patients on AZT + 3TC + NVP are needed to confirm the findings of this study.

In the present study causality assessment based on WHO causality assessment scale, revealed that, 97% of the ADRs were "possible" and 3% were "unlikely". The similar findings were observed by *Aboubacar A. Oumar et al*, in their study. [24] A complete follow up of the patient profile and reaction while collecting ADRs would have established more cases of 'possible' association of the encountered ADRs.

CONCLUSION

Patients are more prone to develop adverse drug reactions (ADRs) to antiretroviral because of the disease process itself or the less studied post marketing safety profiles of the ART drugs. Findings of our study suggest that the treating clinicians must be vigilant towards early detection and prevention of ADRs in HIV infected patients receiving ART so that timely intervention and modification of the given drug regimen will ensure better adherence to antiretroviral therapy. Counselling the patients about common minor toxicities, the warning signs serious toxicity that is skin reactions, jaundice, how to distinguish a self-limiting ADR from that which can be potentially serious is necessary so that severe morbidity and mortality could be avoided. ADR surveillance has to be an essential component of evaluating an ART program to make it more patient compliant. Therefore more proactive pharmacovigilance surveillance is mandatory for better understanding, and timely reporting of ADRs among patients on different ART regimens.

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