

To Assess Causality Using WHO-UMC Criteria & Identify the Offending Drug/Drugs

Dr. Rajkumari Bansal¹, Dr. Inder Dev Ashahiya², Dr. K K Daryani³

¹Postgraduate Student, Department of Pharmacology, NSCB Medical College, Jabalpur, Madhya Pradesh, India

²Assoc. Prof., Department of Anaesthesiology, NSCB Medical College, Jabalpur, Madhya Pradesh, India

³Professor, Department of Pharmacology, NSCB Medical College, Jabalpur, Madhya Pradesh, India

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*Corresponding author
Dr. Inder Dev Ashahiya

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Abstract: This is a prospective as well as retrospective observational study jointly conducted in the Department of Pharmacology and ART centre of N.S.C.B. Medical College Jabalpur M.P. after the approval of Institutional Ethics Committee. 121 (46.5%) patients received TLE regimen, out of which 99 (45%) patients developed ADRs. Maximum 220 (51.7%) ADRs occurred in TLE regimen with the female preponderance of 64% followed by 157 (37%) ADRs due to ZLN. A significant association was found between females' ADR and TLE regimen. 122 (55.5%) ADRs were probable and 98 (44.5%) ADRs were possible by WHO-UMC causality assessment scale.

Keywords: WHO, Drugs, Adverse Drug Reaction

INTRODUCTION

The WHO Collaborating Centre for International Drug Monitoring (IDC) in Uppsala, Sweden manages the international database of adverse reaction reports received from national centres. In 2005 this database held over 3.5 million case reports. The Centre has established standardized reporting by all national centres and has facilitated communication between countries to promote the rapid identification of signals. The terminologies developed within the WHO programme for coding adverse reactions to medicines have been widely adopted by national centres, manufacturers and medicine regulators. More effective communication of information is being promoted and encouraged through the WHO Programme for International Drug Monitoring [1].

Functions of the WHO Programme for International Drug Monitoring include:

- Identification and analysis of new adverse reaction signals from the case report information submitted to the National Centres, and sent from them to the WHO ICSR database. A data-mining approach (IC analysis) is used at the UMC to support the clinical analysis made by a panel of signal reviewers.
- Provision of the WHO database as a reference source for signal strengthening and ad hoc investigations. Web-based search facilities and customized services are available.
- Information exchange between WHICH, UMC and National Centres, mainly through 'Vigimed', an internet based information exchange system.
- Publication of periodicals, newsletters, (WHO Pharmaceuticals Newsletter and Uppsala Reports), guidelines and books in the pharmacovigilance and risk management area.

- Supply of tools for management of clinical information including individual case safety reports. The main products are the WHO Drug Dictionary and the WHO Adverse Reaction Terminology.
- Provision of training and consultancy support to National Centres and countries establishing pharmacovigilance systems.
- Computer software for case report management designed to suit the needs of National Centres (VigiFlow)
- Annual meetings for representatives of National Centres at which current pharmacovigilance issues and the development of the Programme are discussed.
- Methodological research for the development of pharmacovigilance as a science[2].

MATERIAL & METHOD

Ethical clearance from the Institutional Ethics Committee was obtained before starting the study.

CONDUCT OF STUDY

The study was jointly conducted in the Department of Pharmacology & ART centre of N.S.C.B. Medical College, Jabalpur M.P.

DURATION OF STUDY

The study was conducted from March 2016 to July 2017 for data collection, after which data was analysed.

SAMPLE SIZE

In this study the sample size is 260.

SELECTION CRITERIA OF CASES

The participants in this study had been offered to voluntarily participate in the study and they had given written informed consent before they were enrolled in the study.

INCLUSION CRITERIA

- Patients of any age of either sex.
- Both new and old registered patients who were on ART.
- Patients who gave written informed consent.

EXCLUSION CRITERIA-

- Patients who do not give informed consent for participation in the study.
- Patients who were not able to recall or explain the symptoms of ADR.
- Patients unable to respond to verbal questions.

METHOD

After approval from the Institutional Ethics Committee, every enrolled patient who were already on ART and who has newly started the ART during this study period, were observed. These patients were provided with Informed Consent Form and their consent for the study was documented. Details of the participants were kept confidential.

Patient data was collected into two suitably designed forms:

- Patient Proforma.
- CDSCO adverse drug reaction reporting form.

Detailed history of patient including demographic detail, past and present illness, concurrent systemic illness and drug history was taken along with detailed clinical examination when the patient came for follow-up visits to ART centre. These informations were recorded on a pre-designed patient proforma and correlated with prefilled patient treatment records (white card). Essential laboratory investigations like complete blood counts, liver function tests (LFTs), renal function tests (RFTs), lipid profile, blood sugar tests and CD4 count was done or recorded from prefilled patient treatment records.

All the ADRs were duly filled up in the suspected adverse drug reaction reporting form of Central Drugs Standard Control Organization (CDSCO) by interviewing with patient or patients' care taker and by reviewing prefilled patient treatment records. To establish the etiologic agents for ADR, attention was paid to the drug history, speculating the temporal correlation with the drug, duration of ADR, type of reaction, improvement in reaction on withdrawal of drug and recurrence of reaction on rechallenge if possible. These ADR was further assessed for its Causality, Severity and Preventability using WHO-UMC criteria, Modified Hartwig and Siegel scale, and Modified Schumock and Thornton criteria respectively.

DATA ANALYSIS AND STATISTICS

The data were analyzed using SPSS 20. Appropriate univariate and bivariate statistical analysis were carried out using the *Student's t* test for the continuous variable (Age) and two-tailed Fisher exact test or chi-square (χ^2) test for categorical variables. All means and all means are expressed as mean \pm standard deviation and proportion in percentages. The critical levels of significance of the results were considered at 0.05 levels i.e. $p < 0.05$ was considered significant.

TOOLS IN THE STUDY

CDSCO Adverse Drug Reaction Reporting Form

It is an adverse drug event reporting form designed by Central Drugs Standard Control Organization (CDSCO), Director General of Health Services; Govt. of India for voluntary reporting of Adverse Drug Events by health care professional. It is divided in 5 sections:

- Patient Information
- Suspected Adverse Reaction
- Suspected Medications
- Clinician (If not reporter)
- Reporter.

After filling the form, it should be submitted to the Peripheral Pharmacovigilance centre which then forwarded to National Pharmacovigilance centre through the Regional and Zonal Pharmacovigilance centre after the causality assessment. Finally the information is reported to WHO-Uppsala Monitoring Centre, Sweden.

WHO-UMC scale for causality assessment [3]

The WHO- UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical pharmacological aspects of the case history and the quality of the documentation of the observation.

According to this scale, adverse drug events are classified in to 6 categories:

- Certain / Definite
- Probable / Likely
- Possible

- Unlikely
- Conditional
- Unassessible

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	<ul style="list-style-type: none"> • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with.

OBSERVATION & RESULTS

Table-1: Drug regimens and patients found with ADRs

REGIMEN	TOTAL PATIENTS (n=260) (%)	ADR (+) PATIENTS (n=220) (%)	TOTAL ADRs (n=425) (%)
ALN	8 (3.1)	7 (3.2)	8 (1.9)
SLN	21 (8.1)	17 (7.7)	22 (5.2)
TLE	121 (46.5)	99 (45)	220 (51.7)
TLN	8 (3.1)	7 (3.2)	10 (2.3)
ZLE	5 (1.9)	5 (2.3)	8 (1.9)
ZLN	97 (37.3)	85 (38.6)	157 (37)

$$\chi^2 = 2.63; p > 0.05 \text{ at } 5df$$

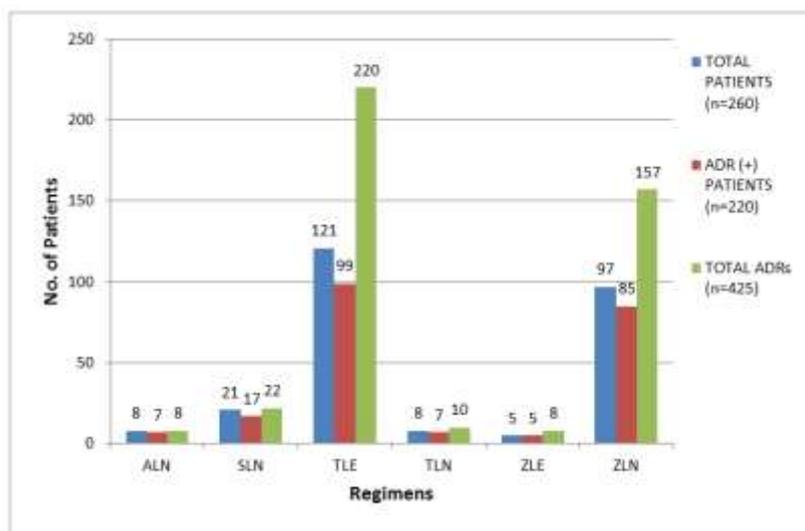


Fig-1: Drug regimens and patients found with ADRs

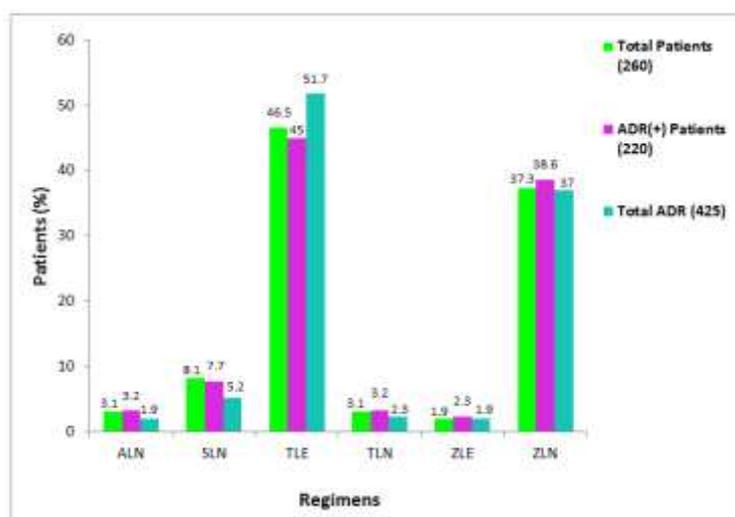
Table-2: Drug regimens and patients found with ADRs

REGIMEN	TOTAL PATIENTS (n=260) (%)	ADR (+) PATIENTS (n=220) (%)	ADR (-) PATIENTS (n=40) (%)	TOTAL ADRs (n=425) (%)
ALN	8 (3.1)	7 (3.2)	1 (2.5)	8 (1.9)
SLN	21 (8.1)	17 (7.7)	4 (10)	22 (5.2)
TLE	121 (46.5)	99 (45)	22 (55)	220 (51.7)
TLN	8 (3.1)	7 (3.2)	1 (2.5)	10 (2.3)
ZLE	5 (1.9)	5 (2.3)	0 (0)	8 (1.9)
ZLN	97 (37.3)	85 (38.6)	12 (30)	157 (37)

$\chi^2 = 2.63; p > 0.05$ at 5df

This table shows distribution of patients and ADRs with particular regimens. 260 patients were enrolled out of which 220 patients developed a total of 425 ADRs. ADRs were observed in 45% and 38.6% of patients who were on regimen TLE and ZLN

respectively. Maximum 51.7% ADRs were caused by TLE followed by 37% with ZLN regimen. The association between the presences of ADRs among patients with different regimens was statistically not significant.



Graph- 2: Drug regimens and patients found with ADRs

Table-3: System wise ADRs with regimens

SYSTEM	REGIMEN						TOTAL (% of ADR)
	ALN (n=8)	SLN (n=22)	TLE (n=220)	TLN (n=10)	ZLE (n=8)	ZLN (n=157)	
CNS	0	6	121	1	0	14	142 (33.4)
GIT	0	2	44	0	2	30	78 (18.4)
Hepato-renal	0	1	14	0	0	5	20 (4.7)
Dermatological	7	9	18	8	0	49	91 (21.4)
Haematological	1	0	0	0	6	52	59 (13.9)
Others	0	4	23	1	0	7	35 (8.2)

425 ADRs occurred in 220 patients with the involvement of various systems by different regimens. Majority 33.4% experienced CNS effect followed by dermatological 21.4%, GIT 18.4%, haematological

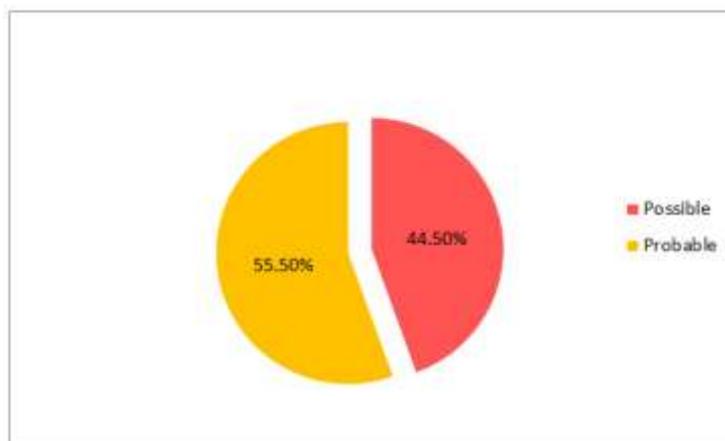
13.9% and 8.23% other types of ADRs. CNS and GIT ADRs mostly occurred in TLE and ZLN regimens. Dermatological and haematological adverse reactions occurred mainly in ZLN regimen.

Table-4: Causality assessment

CAUSALITY ASSESSMENT	NO. OF PATIENTS (N=220)	PERCENTAGE (%)
Possible	98	44.5
Probable	122	55.5

Table 4 shows causality assessment as per WHO-UMC causality scale. 98 (44.5%) patients, among a total of 220, had possible affiliation to the

offending drug while 122 (55.5%) patients had probable association to the drugs.



Graph – 4: Causality assessment

DISCUSSION

Most of them were housewife (37.3%) followed by labourer (20.4%). Tadesse *et al.* [9] study is in concordance with our study where they found majority of the patients to be unemployed (64.2%).

Mostly married patients (67%) were found in our study which is similar to Lartey *et al.* [8] where 50.5% patients were married. Maximum number of patients (79.6%) had infection by heterosexual mode of transmission which is corroborated by Reddy *et al.* [7] where they found 87.3% patients to be infected by heterosexual mode.

In our study, 6 types of regimens were employed among the study population. Abacavir (A), Stavudine (S), Tenofovir (T) and Zidovudine (Z) based treatment was used with the combination of

Lamivudine (L) and Nevirapine/Efavirenz (N/E). Most of the patients received TLE (46.5%) regimen followed by ZLN (37.3%), SLN (8.1%), ALN (3.1%), TLN (3.1%) and ZLE (1.9%). Similar finding was found by Jain *et al.* [13] where 83% patients received TLE regimen followed by ZLN (10%) regimen. Among those who reported ADRs, 45% were on TLE, 38.6% on ZLN, 7.7% on SLN, 3.2% each on ALN and TLN, and 2.3% on ZLE regimen. Out of total 425 ADRs, 51.7% occurred in patients who were on TLE regimen, 37% in the patients on ZLN regimen and remaining by others regimens. This is in accordance with Kumar *et al.* [11] where maximum ADRs amounting to 49.23% and 23.85%, were observed with patients on TLE and ZLN regimen respectively. Sehgal *et al.* [14] too showed similar findings.

Out of the total 425 ADRs, 41% were observed in males and 59% in females. Maximum ADRs (51.7%) occurred in TLE regimen with the female preponderance of 64%. Similar findings were also observed by Eluwa *et al.* [6] where out of 114 ADRs reported, 64.04% occurred with female preponderance. But our study is in contrast to the study of Khan *et al.* [12] who showed male preponderance of ADRs with 73.1%.

Major organ systems involved in our study were: central nervous system (CNS) 33.4% followed by dermatological 21.4%, gastrointestinal (GIT) 18.4%, haematological 13.9%, hepato-renal 4.7% and 8.2% others. This is in accordance to Jain *et al.* [13] where they found that majority of ADR were related to CNS (40.3%) followed by GIT (37.5%). Lorio *et al.* [10] study too endorsed with our study who found that 45.5% of ADRs were pertaining to central nervous system, 27.3% to gastrointestinal and 18.2% dermatologic. But Sharma *et al.* [4] observed cutaneous ADR (44.4%) as the most common ADR followed by haematological (32.2%) and CNS (31.1%) while Takaki *et al.* [15] observed gastrointestinal disorders (25.9%) as the most common ADR. Nagpal *et al.* [5] observed that most common ADR were related to GIT (42.4%) and CNS (25.6%). Regarding CNS effects, majority of ADRs were due to TLE regimen in our study. Similar finding were also seen by Sehgal *et al.* [14] where maximum (38.7%) ADRs were of CNS due to TLE regimen.

CONCLUSION

The TLE regimen prescribed as per WHO and NACO guidelines cause mainly CNS ADRs, especially with efavirenz. These ADRs were mild to moderate in nature and subside spontaneously after 2-3 weeks without discontinuing the treatment. Maximum ADRs were managed by counselling and or symptomatically. Some drugs like zidovudine and stavudine show ADRs such as anaemia, neutropenia and peripheral neuropathy after long term treatment. So an active pharmacovigilance is needed for identification, prevention and management of such ADRs developed by ART. This ensures not only safety of the patients but also compliance to the treatment which is necessary for optimal therapeutic outcomes and to improve quality of life.

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