Original Research Article

Characterization and comparative analysis of ADRs of various ART regimens: experience of our medical college from Western Himalayan region

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ABSTRACT

Background: It is estimated that there are 35.3 million PLHA worldwide and 1.6 million have received ART. ART is freely available in designated ART Centres. HAART (highly active antiretroviral treatment) has significantly reduced AIDS related morbidity and mortality. It involves using three different drugs from two different classes. The main challenge in prescribing HAART is ADRs associated with it affecting patient compliance and treatment outcomes.
Methods: A retrospective observational study was carried out in the ADR monitoring Centre of Dr. Rajendra Prasad Government Medical College, Tanda, Kangra, Himachal Pradesh, India.
Results: The data for ADEs was collected from 108 patients over a period of 17 months. A total of 280 ADEs were reported in 65 females and 43 males. TLE was the commonest regimen in 61 (56%) patients followed by ZLN in 37 (34%). Neurological ADRs were reported in 39.8% cases with TLE that was nearly double as reported with ZLN regimen 20.5%. Dermatological ADRs were highest with other regimens (57.4%) followed by ZLN 20.5%. Similarly the frequency of Gastrointestinal ADR was highest with other regimens. Hematological ADRs were maximum with ZLN (22.9%) followed by TLE (3.3%). Most commonly reported ADRs were dizziness (10.7%), rashes (8.2%), anorexia and dyslipidemia (6.8%), asthenia (6.4%), pruritus (6%), joint pains (4.6%), insomnia, alopecia and vomiting (4.3%), numbness or parasthesia (3.9%), hepatotoxicity (3.6%) and deranged RFTs (1.8%).
Conclusions: The real burden of ADRs due to ART cannot be estimated until voluntary and mandatory reporting system of ADRs works efficiently. A structured surveillance of the pharmacovigilance system can help to overcome these hurdles to ensure compliance with ART regimens.

Keywords: ART, ADRs, NACO, Pharmacovigilance

INTRODUCTION

ART (antiretroviral therapy) for the treatment of people living with HIV and AIDS (PLHA) under NACO (National AIDS Control Organization) is freely available in designated ART centers and has contributed in prolonging survival. ART works by suppressing the viral load and restoring the immune system. The scientific community has come a long way from the first drugs available for HIV in 1986 as Zidovudine (AZT) and didanosine (ddl) in early 1990s to now an armatorium comprising of more than 25 drugs from six different classes. The introduction and availability of highly active anti-retroviral therapy (HAART) has translated to significant reduction of AIDS-related morbidity and mortality. HAART involves using at least three different drugs from two different classes. It has been estimated that out of the 35.3 million PLHA worldwide, 10.6

million received ART in 2012 and nearly 6.6 million AIDS related death have been prevented with ART.[1] This tremendous success with HAART has resulted in transforming this life threatening illness to a chronic condition.

Nevertheless challenges persist as HAART is fraught with high risk of adverse drug reactions (ADRs) and consistent use is required to prevent viral drug resistance and meet treatment goals. High percentage of ADRs deter the patients from taking regular medication, and drug withdrawal or discontinuation results in treatment failures.[2] Lack of adherence to treatment can have grave consequences with implications both for the individual patient and community.[3] At the patient level non adherence to ART can lead to adverse HIV related outcomes in terms of viral load, CD4 cell count, increased opportunistic infections, and progression to AIDS and survival.[4,5] For the community non-adherence to ART may increase viral resistance to antiretroviral drugs and transmission of drug-resistant strains of HIV.[6] Knowledge of antiretroviral toxicities is a prerequisite for choosing an appropriate regimen among many possible combinations in HAART.

ADRs to ART may arise either due to effect of disease on the immune system or the safety profile of ART combinations.[7] ADRs in developing countries differ from those of developed world because of the high prevalence of conditions such as malnutrition, anemia, tuberculosis and patients presenting with advanced HIV disease.[8] ADRs may be common or specific to a class of drug. Among nucleoside reverse transcriptase inhibitors (NRTI) two or more form the "backbone" of antiretroviral (ARV) regimens. Zidovudine (AZT) and Stavudine (d4T) are known to cause anemia, nausea, rashes, lipodystrophy and lactic acidosis.[9] Didanosine (ddl), Stavudine (d4T) and Zalcitabine (ddC) are known to cause pancreatitis, peripheral neuropathy and oral ulcerations, hence not co-prescribed.[10]

Drugs classified as non-nucleoside reverse transcriptase inhibitors (NNRTI) which include Nevirapine (NVP) and Efavirenz (EFZ) are known to cause rashes and hepatotoxicity, while both Efavirenz and Delavirdine (DLV) are teratogenic and avoided in pregnancy. Another important group of protease inhibitors (PI) result in syndrome of redistribution and accumulation of body fat resulting in central obesity with concurrent increase in triglyceride and LDL levels along with glucose intolerance.[10] ADRs also depend on the patient age, gender, CD4 cell counts and other comorbidities. Rashes are common in early treatment with NVP in females and may be severe enough to cause Steven-Johnson Syndrome or Toxic epidermal necrolysis. Similarly risk of hepatotoxicity is greater in females, with higher pretreatment CD4 cell counts and HBV or HCV co-infection.[10] ADRs to ART can be predictable due to myriad of drug-drug interaction; some could be pharmacodynamics or pharmacokinetic resulting in additive toxicities or therapeutic failure. Many clinically significant interactions occur during metabolism by cytochrome P450, a family of enzymes responsible for oxidative metabolism of majority of ARV drugs including NNRTIs, PIs, chemokine co-receptor 5 antagonists Maraviroc.

NRTIs are intracellular active molecules that have relatively few drug interactions. Among the NNRTIs, Delavirdine is a potent CYP3A4 inhibitor, while Nevirapine is a potent CYP3A4 inducer. Efavirenz and Etravirine exhibit a mixed CYP3A4 induction/inhibition pattern. Among the PIs all are substrates for cytochrome P450, inhibiting CYP3A4 to varying degrees and interacting with other drug classes like antifungals, anti-mycobacterial, statins, anticonvulsants, oral contraceptive and PPIs (Proton pump inhibitors).[11]

Of all the PIs Ritonavir is the most potent CYP3A4 inhibitor and this feature is exploited to bolster the plasma levels of other PIs ("ritonavir boosting").[12] PIs such as darunavir, tipranavir, and lopinavir must always be boosted with ritonavir to achieve effective plasma levels. Keeping in view the above considerations, monitoring and reporting of ADRs to ART assumes significance as there was paucity of data from our region and hence the present study was planned.

ADR reporting in our hospital started in 2015 under the Pharmacovigilance Program of India (PvPI). ADRs themselves are defined by WHO as an unintended and noxious response to a drug that occurs at doses normally used for the prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological function.[13] ADRs themselves add to work loss, hospitalization costs, morbidity and mortality.

Aims and objectives

The purpose of this study was to detect and characterize the commonly encountered ADRs among patients on antiretroviral therapy (ART) in Dr. Rajendra Prasad Government Medical College, Tanda, Kangra, Himachal Pradesh, India.

METHODS

The study was conducted at ADR monitoring center (AMC) of Dr. Rajendra Prasad Government Medical College, Tanda, Kangra, Himachal Pradesh, India a 585-bedded rural tertiary care teaching hospital after approval from institutional ethics committee. This was a retrospective observational study. Data collection was done through voluntary reporting by health-care professionals (HCP) in standard IPC-PvPI prescribed suspected ADR reporting form and analyzed for 108 patients on ARV regimens from April, 2015 to August 2016. Causality assessment of ADEs was done by causality assessment committee using WHO causality assessment scale.

RESULTS

Data analysis was done for 108 patients over a period of 17 months in the ART Centre of our medical college. Total 280 ADEs were observed in these patients. Among 108 patients, 65 were females and 43 were males. The mean age in female patients was 39.4±11.9 (SD) with a mean weight of 48.3±12.25 (SD). Among the male patients the mean age was 39.3±12.1 (SD) with a mean weight of 48.4±12.59 (SD). Among the female patients we had four outliers in the pediatric age group (one girl of 4 years, one girl of 8 years and two girls of 9 years each). None of the male patients were children.

ARV Regimens

Data analysis was done according to the ARV regimens prescribed and observed that TLE (TDF+3TC+EVF) was the commonest with 61 patients and accounted for 178 ADEs. ZLN (AZT+3TC+NVP) was next in the order of frequency with 37 patients accounting for 83 ADEs.

Other regimens were implicated in 10 patients and accounted for 19 ADEs. These included ZLE (AZT+3TC+EFZ), TLN (TDF+3TC+NVP), SLN (d4T+3TC+NVP), ALE (ABC+3TC+EVF) and ALN (ABC+3TC+NVP).
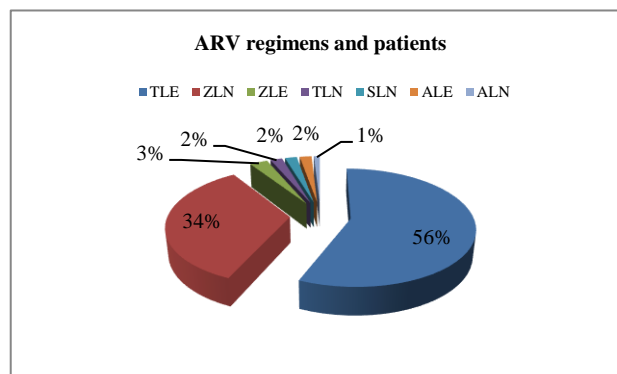

Figure 1: Depicting the various ARV regimens and the quantum of patients (n=108).

Table 1: ADEs according to the organ system involvement.

Organ system involvement	Symptoms	TLE (n=61) 178 ADEs	ZLN (n=37) 83 ADEs	Others (n=10) 19 ADEs ; ZLE, SLN, TLN, ALE
Neurological	Dizziness, headache, insomnia, numbness, irritability, amnesia, confusion	71 (39.8%)	17 (20.5%)	1 (5.2%)
Dermatological	Pruritus, rashes, alopecia, SJ Syndrome, nail discoloration	28 (15.7%)	17 (20.5%)	11 (57.9%)
Gastrointestinal	Anorexia, deranged LFTs, nausea, vomiting, diarrhea, oral ulcers	34 (19.1%)	17 (20.5%)	5 (26.3%)
Hematological	Dyslipidemia, anemia	6 (3.3%)	19 (22.9%)	0 (0%)
Others	Asthenia, joint pains, fever, deranged RFTs, weight loss, lipodystrophy, menstrual irregularity	39 (21.9%)	13 (15.6%)	2 (10.5%)

Maximum numbers of neurological ADRs were reported with TLE regimen and this was double the percentage of ZLN regimen. Equivalent percentages of gastrointestinal ADRs were observed with both TLE and ZLN regimen. ADRs affecting the hematological system formed the majority of ADRs with ZLN regimen. Similarly the dermatological ADRs the most common ADRs observed with other treatment regimens under HAART. Further sub-analysis of the ADEs observed was done (Figure 2).

The commonest ADEs reported were dizziness, followed by rashes, dyslipidemia, anorexia, asthenia and pruritus in decreasing frequency. Some rare ADEs observed in our study were vertigo, drowsiness, depression, irritability and tremor. Rare dermatological ADEs included nail discoloration, Steven Johnson Syndrome, and petechiae.
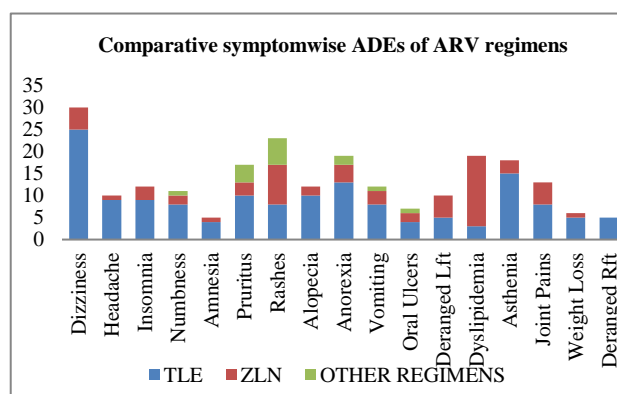

Figure 2: Various ADEs according to the ARV regimen and their comparative frequency.

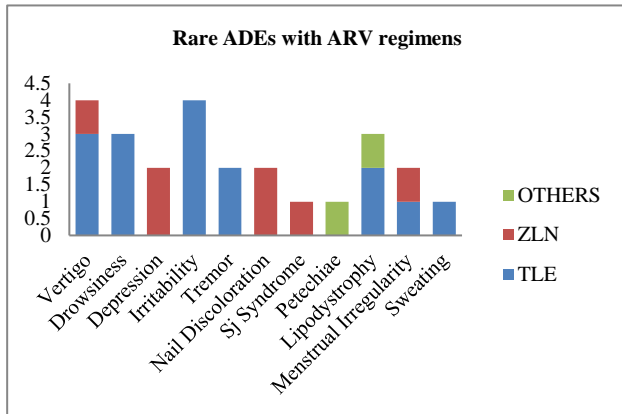ADEs involving other systems included lipodystrophy, menstrual irregularity and sweating (Figure 3).

Figure 3: Rare ADEs observed with ARV regimens.

Data was further analyzed in terms of time latency for ADEs to manifest, seriousness of ADEs and causality assessment. Majority of the ADEs were sub-acute to chronic in onset and similar findings were observed with all the three ARV regimens.
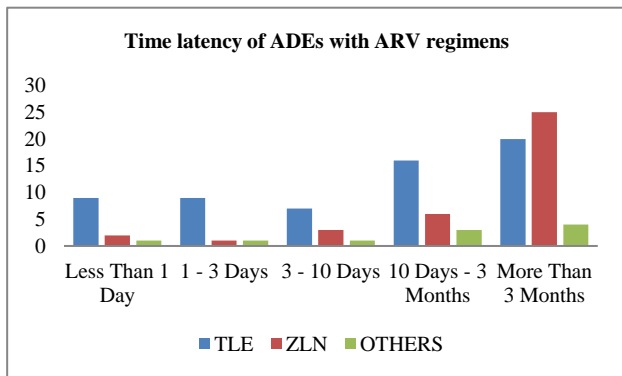

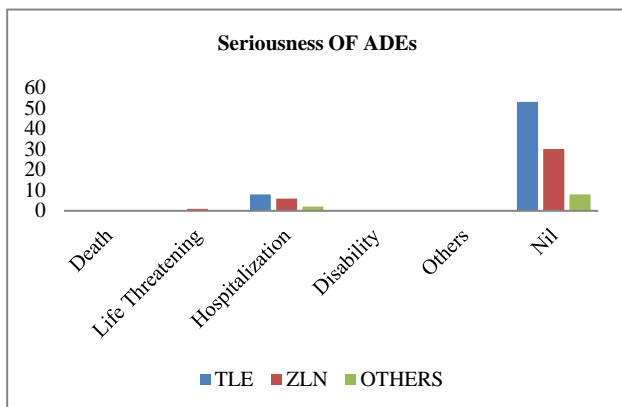**Figure 4: Time latency for ADEs to manifest.**

Figure 5: Seriousness of ADEs among the patients.

As regards to the seriousness of ADEs an overwhelming majority were non serious requiring no intervention, treatment or hospitalization. One case of Steven Johnson

Syndrome (SJS) was encountered with ZLN regimen which was life threatening and promptly recovered with therapy. Causality assessment of ADEs was done by the causality assessment committee of the hospital (Figure 6). Majority of the cases were possible (64) and probable (42) in nature and certainty could be ascribed only to two cases.
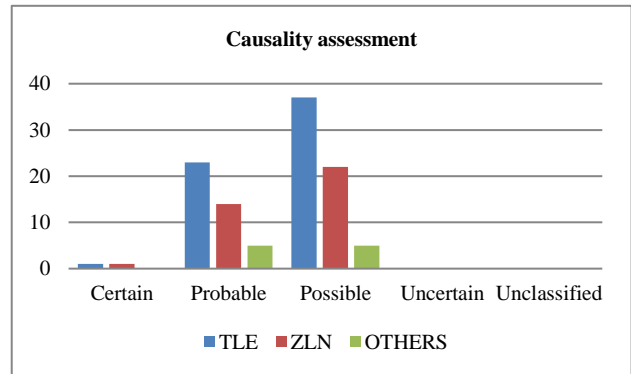

Figure 6: Causality assessment of ADRs among the patients on ART regimens.

DISCUSSION

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, reporting and prevention of adverse effects or any other drug-related problem.[14] The main emphasis of pharmacovigilance is to detect signals generated as adverse drug events (ADEs) and to establish their causality so as to label them with certainty as adverse drug reactions (ADRs).[15] A total of 280 ADEs were observed in 108 patients with an overall prevalence of 260% which is in concordance with Nagpal et al (263%).[16] Females (60%) outnumbered males (40%) and this is in concurrence with a South African study.[17]

Efavirenz based regimens accounted for 61% cases while the rest were nevirapine based. Neurological ADRs were predominant in patients on TLE and included dizziness, headache, insomnia, numbness and amnesia in about 40% and double of what was observed with ZLN. This was not surprising and can be explained by the fact that both tenofovir and lamivudine are known to cause dizziness.[10] The principal toxicity associated with efavirenz is neurological and this explains the fact of high incidence of neurological ADRs with TLE regimen. Lamivudine was part of HAART in all patients and is one of the least toxic anti-retroviral drugs.[18] However; the chief ADRs observed with ZLN were hematological (23%) which included dyslipidemia and anemia. Similar frequencies of neurological, gastrointestinal and dermatological ADRs (20.5%) were observed with ZLN. This was in contrast to other regimens where an overwhelming majority of ADRs were dermatological (58%).

In present study the most commonly reported ADRs were dizziness (10.7%), rashes (8.2%), anorexia and

dyslipidemia (6.8%), asthenia (6.4%), pruritus (6%), joint pains (4.6%), insomnia, alopecia and vomiting (4.3%), numbness or parasthesia (3.9%), hepatotoxicity (3.6%) and deranged RFTs (1.8%). These results are in agreement with Nagpal et al. who reports incidence of skin rash (7.45%) and hepatotoxicity (3.19%) and much lower in comparison to that reported by Rotunda et al. (skin rash-15%), Martinez et al. (hepatotoxicity-12.5%) and Sulkowski et al. (hepatotoxicity- 15.6%).[16,19-21] In present study we observed anemia in both TLE and ZLN regimens (3 each) with a combined frequency of 2.1%. This is total disagreement with a Jodhpur study which reports anemia-(16%) as the commonest ADR followed by gastritis (8.5%), rashes (6.4%), vomiting (5.8%), pruritus (5.3%), and leucopenia (4.2%).[22] Zidovudine is known to cause bone marrow suppression leading to anemia and thrombocytopenia. Present study is in partial agreement with a Guwahati study which reports common ADRs with ART as gastritis (13.1%), rashes (8.7%), anemia (8.1%), dizziness (6.9%), anorexia (6.9%) and parasthesia of legs as 3.75%.[23]

Nevirapine is commonly associated with dermatological ADRs like skin rash and pruritus. Six patients in our study had a prior history of sensitivity to nevirapine and were changed to efavirenz based regimens. We observed one patient with SJS in present study on ZLN who developed diffuse, exfoliating exanthema with generalized bullous eruptions all over the body. This patient was saved from this life threatening medical emergency by satisfactory drug de-challenge and prompt therapy. Low incidence of peripheral neuropathy and numbness in our study is due to the fact that peripheral neuropathy is usually associated with stavudine (d4T), zalcitabine (ddC) and didanosine (ddl) use and a declining trend to use these drugs. Latest WHO updates do not recommend use of stavudine as a first line drug for ART.[24]

We observed five patients who had pulmonary tuberculosis as co-infection. The association between HIV and TB is bidirectional. HIV infection increases the risk of both primary and reactivation TB, and this risk increases tremendously with advanced HIV disease.[25] Prior observational studies have found that the concurrent use of HAART in patients co-infected with TB have significant mortality benefits.[26,27] Problems of drug interactions, overlapping drug toxicities and higher pill burden complicate concomitant HAART with TB therapy and these have been argued for deferred initiation of HAART during TB treatment.[28] The American Thoracic Society, Centre of Disease Control and Prevention (CDC) TB treatment guidelines as well as current expert opinion suggest that ART should be delayed for 4-8 weeks after starting ATT (anti-tuberculosis therapy) so as to allow better evaluation of drug side effects, reduce the severity of paradoxical reactions, and compliance of patients.[28] In patients with CD4+ cell-counts <100/µl or advanced AIDS, initiation of concurrent HAART must be considered as early as possible. In our study two patients

had ATT prior to HAART, in two patients both HAART and ATT was started on same day and one patient had HAART initiated before commencing ATT. The interactions between rifamycins with NNRTIs and PI are complex with difference in the capacity to induce expression of CYP3A4 isozyme in liver and intestine. As both NNRTIs and PI are metabolized by CYP3A4, rifampicin reduces area under curve (AUC) of EFZ by 22-26% and of NVP by 31%.[29,30] This results in HIV treatment failure and emergence of drug resistance. Rifabutin is a less potent inducer of CYP3A4 than rifampicin and does not result in significant changes in plasma EFZ concentrations and reduction of NVP levels by only 16%, hence not necessitating dose adjustments of EFZ or NVP with concurrent ATT administration.[31] Non availability and high cost of rifabutin based ATT in a resource poor setting precludes its use as none of the above patients received it.

We also observed few cases of deranged RFTs, irritability, drowsiness and tremors exclusively with TLE regimen. It was again unsurprising as tenofovir is associated with renal drug clearance with recommended dosage adjustments. Few cases of weight loss can be explained either by EFZ, primary disease or concomitant opportunistic infections. Some rare ADRs observed exclusively with ZLN include depression, nail discoloration and SJS. Few earlier mentioned studies often mention nail discoloration as an important long term ADR but in our study we found it with a frequency of 0.7%. Some other rare ADRs were also observed as menstrual irregularity and sweating.

Causality assessment of cases was done by using WHO causality assessment scale and it revealed that majority of cases were possible (59.2%) followed by probable cases (38.8%). Certainty was ascribed only to two cases (1.8%). Re-challenge was not attempted in any of the cases due to ethical issues. Our findings are in coherence with previous studies which underline the fact that possible ADRs outnumber probable ADRs by a ratio of 3:2.[22,23]

Study Limitations

In India, several patients also take AYUSH (Ayurveda, Unani, Sidhha and Homeopathy) therapies concurrent to allopathic treatments which often contain heavy metals. Drug interactions with these alternative systems of medicine in India are often unreported and may lead to alteration in outcomes of drug reactions.[15]

More such studies are required with more number of patients to pick up rare ADRs. Efforts should also be made for mandatory reporting of ADRs as voluntary reporting is very inefficient system for drug related problems leading to underestimation of the burden due to ADRs. Hence more systematic and robust monitoring methods as structured surveillance pharmacovigilance systems, which assess and monitor safety profile of

antiretroviral drugs is advocated as myriads of ADRs entail compliance issues and impact treatment outcome.

CONCLUSION

The real burden of ADRs due to ART cannot be estimated until voluntary and mandatory reporting system of ADRs works efficiently. A structured surveillance of the pharmacovigilance system can help to overcome these hurdles to ensure compliance with ART regimens.

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