Original Article

A safety analysis of different drug regimens used in human immunodeficiency virus-positive patients

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Abstract

Background: Long-term toxicity of antiretroviral agents is rarely addressed in initial clinical trials. Effective pharmacovigilance is essential for long-term safety of antiretroviral therapy (ART). **Materials and Methods:** All adverse drug reactions (ADRs) reported due to ART between January 2014 and September 2016 were analyzed as per different drug regimens used. ADRs were also analyzed for system organ classification, seriousness, time relationship of ADRs with drug therapy, causality (as per the World Health Organization-Uppsala Monitoring Centre scale and Naranjo algorithm), and severity (Hartwig and Siegel scale). Comparison was done between (tenofovir + lamivudine + efavirenz [TLE]) and (zidovudine + lamivudine + nevirapine [ZLN]) regimens. **Results:** During a study period, 2983 patients were on ART. The most common drug regimen prescribed was TLE (1805) followed by ZLN (326). A total of 325 (10.89%) ADRs were reported in which 150 ADRs were reported in TLE regimens (46%) and 130 in ZLN regimens (40%). The mean age of patients with ADRs was 40 ± 12.56 years and men (58.1%) were more affected than women (41.8%). The most common system organ involved in ZLN regimen was blood (50, 39%) and skin (35, 27%), while it was neurological (63, 42%) and renal disorder (27, 18%) in TLE regimen. Most of ADRs were observed after 1 month of therapy (79.5%) and showed possible causal relation with drug therapy (78.15%). Majority of ADRs were mild in nature (86.7%). The serious ADRs were reported more in ZLN (18%) regimen as compared to TLE (9%) ($P < 0.05$). **Conclusion:** Both ART regimens are associated with ADRs affecting all body system; however, the frequency and severity of ADR are high with ZLN regimen.

Keywords: Adverse drug reactions, antiretroviral therapy, pharmacovigilance

INTRODUCTION

Human immunodeficiency virus (HIV)/AIDS is world's sixth largest cause of death in humans, accounting for 3.1% of all deaths.[1] World over 36.7 million people are living with HIV. Of these, 17 million people are on antiretroviral therapy (ART).[2] The advent of highly active ART has been a boon for HIV-infected patients by reducing morbidity and extending life span.[3] Over the last decade, ART in low- and middle-income countries has saved an estimated 4.2 million lives and prevented an estimated 800,000 child infections.[4] The annual number of AIDS-related deaths has declined by 54% during 2007–2015.[5] These ARTs are given in various combinations as different regimens to prevent the resistance and for better efficacy outcome. Most of these patients are treated with recommended first-line drug regimen (tenofovir + lamivudine + efavirenz [TLE])

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or alternative first-line drug regimen (zidovudine + lamivudine + nevirapine [ZLN]) as per the recent National Aids Control Organization (NACO) guidelines.[6] Each class of ARV drugs has the potential to cause toxicities, many of which are shared by drugs likely to be used concomitantly in HIV-positive patients. This complicates the treatment, causes difficulty in causality assessment, and may require treatment withdrawal in serious life-threatening reactions.[7] Long-term toxicity of antiretroviral agents is rarely addressed in initial clinical trials. Effective pharmacovigilance is essential for long-term safety of ART.[8] Since there is a paucity of data on safety comparison of ART regimens, this study was taken with objective of safety comparison of the different ART regimens.

MATERIALS AND METHODS

The Pharmacovigilance Programme of India (PvPI) has been launched since July 2010. The Department of Pharmacology and ART Centre, Civil Hospital, is a recognized Adverse Drug Reaction Monitoring Centre. The suspected adverse drug reactions (ADRs) were diagnosed by treating consultants, and relevant details of each ADR were collected in the Central Drugs Standard Control Organization approved spontaneous ADR reporting form.[9] Each ADR report was sent to the National Coordinating Centre through "VigiFlow." Details of each report were also simultaneously entered in Microsoft Excel sheet. All adverse reactions reported because of antiretroviral drug were identified from this database (January 2014 to September 2016). We also have information about number of patients started on ART in similar time period. Data were divided as per different drug regimens used which included TLE, ZLN, atazanavir + lamivudine + efavirenz, and abacavir + lamivudine + atazanavir/ritonavir. The data were analyzed on comparing these different ART regimens by demographic details such as age, gender preponderance, system organ affected, causal drug regimens, and lag period between regimen started and reaction appeared. We have also done causality assessment using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale and Naranjo algorithm, and severity was assessed using modified Hartwig and Siegel.[10-12] Data were analyzed using Chi-square test.

$P < 0.05$ was considered statistically significant.

RESULTS

During a study period, 2983 patients were on ART. The most common drug regimen prescribed was TLE followed by ZLN in which 1805 patients received TLE regimen and 326 received ZLN regimen. A total of 325 (10.89%) ADRs were reported in which 150 ADRs were reported in TLE regimens (46%) and 130 in ZLN regimens (40%). Remaining 45 ADRs were reported due to atazanavir/ritonavir (13), nevirapine (8), co-trimoxazole (6), stavudine + lamivudine + nevirapine (SLN) (6), lopinavir/ritonavir (3), abacavir (2), abacavir + lamivudine (3), abacavir + lamivudine + atazanavir/ritonavir (2), tenofovir + lamivudine + atazanavir (1), and zidovudine + lamivudine + lopinavir/ritonavir (1).

Demography

The mean age of patients suffering from HIV ADRs was 40 ± 12 years (mean ± standard deviation [SD]). The mean age of patients on ZLN and TLE regimens was 41 ± 12.14 years (mean ± SD) and 40 ± 12.56 years (mean ± SD), respectively [Table 1]. The mean weight of patients who developed ADR was 53 ± 11 kg (mean ± SD) and it was almost similar in ZLN and TLE regimen [Table 1]. A maximum number of ADRs were reported in the age group of 38–48 years (33.2%) followed by 27–37 years (31.6%). Men (58.1%) were more affected than women (41.8%).

System-organ involvement

These ADRs have affected most of the body systems [Figure 1]. The most common were skin and appendage disorders (22%) followed by neurological disorders (20%) and blood disorders (18%). The most common system organ involved in ZLN regimen was blood (50, 39%) and skin (35, 27%) while it was neurological (63, 42%) and renal disorder (27, 18%) in TLE regimen.

While the most common ADRs observed were anemia (17.53%) followed by rash and dizziness, we have reported few rare ADRs such as renal toxicities and also liver toxicities [Table 2].

Causal drugs responsible for adverse drug reaction

We have seen that in ZLN regimen, most of patients developed ADRs (40%) as compared to TLE (8%) ($P < 0.001$). One hundred and fifty (46.15%) ADRs are reported with tenofovir-based regimen and 130 (40%) ADRs with zidovudine-based regimen [Figure 2]. Most of renal toxicities are reported with the TLE regimen (87%) while liver toxicities with TLE (23%) and atazanavir-based regimen (77%).

Table 1: Comparison of zidovudine + lamivudine + nevirapine and tenofovir + lamivudine+efavirenz

Parameter	ZLN (*n*=130)	TLE (*n*=150)
Mean age (years), mean±SD	41±12.14	40±12.56
Mean weight (kg), mean±SD	53±10.34 kg (mean±SD)	54±10.84
SOC	Blood disorders=50 Skin and appendage disorders=35 Gastrointestinal disorders=14 Musculoskeletal disorders=12 Body as whole general disorders=7 Psychiatric disorders=7 Neurological disorders=2 Liver and biliary disorders=1 Metabolic disorders=1	Neurological disorders=63 Renal disorders=27 Skin and appendage disorders=22 Gastrointestinal disorders=13 Psychiatric disorders=8 Blood disorders=6 Liver and biliary disorders=4 Body as whole general disorders=3 Musculoskeletal disorders=2 Metabolic disorders=0
Lag time between ADR development and initiation of therapy	<1 week=2 1 week-1 month=13>1 month=115	<1 week=11 1 week-1 month=27>1 month=112
Dechallenge	Dechallenge was done in 28 patients. Positive in 3 patients	Dechallenge was done in 16 patients. Positive dechallenge in 9 patients
Serious	23 ADRs (18%) were serious and required intervention	14 ADRs (9%) were serious and required intervention
WHO-UMC category	Definite=1 Probable=20 Possible=104 Unlikely=5	Definite=2 Probable=22 Possible=125 Unlikely=1
Naranjo category	Probable=31 Possible=99	Probable=29 Possible=119 Definite=2

ZLN=Zidovudine + lamivudine+nevirapine; ADR=Adverse drug reactions; TLE=Tenofovir + lamivudine+efavirenz; SD=Standard deviation; UMC=Uppsala Monitoring Centre; WHO=World Health Organization; SOC=System organ classification

Causality and severity assessment

Majority of ADRs were categorized as possible (74.76%) followed by probable (24.61%) as per the Naranjo algorithm. The WHO-UMC scale also showed majority of ADR were in possible category (78.15%) followed by probable (18.76%). When comparing the regimens, it was seen that in both the regimens, causal relationship was possible (80% ZLN and 83% TLE). Majority of ADRs were mild in nature (282, 86.7%) while 4.9% were moderately severe and 8.3% were severe in nature.

Time relationship of adverse drug reaction with drug therapy

Most of the ADRs (79.5%) were observed on prolonged treatment (>1 month). This includes blood disorders, renal disorders, liver and biliary disorders, and neurological disorders. However, few ADRs were also observed in the 1st week of therapy which includes skin and appendage disorders, gastrointestinal disorders, and neurological disorders [Figure 3].

Gastrointestinal disorders, skin and appendage disorders, and musculoskeletal disorders were observed on initiation of therapy with ZLN, whereas gastrointestinal disorders and neurological and skin disorders were observed on initiation of therapy with TLE.

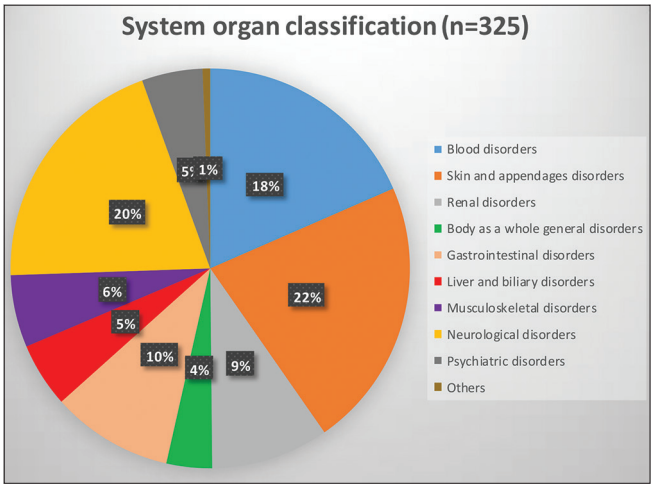

Figure 1: System organ affected because of ART. Others include hearing, vestibular, and special sense disorders and metabolic and nutritional disorders

Seriousness

Majority of ADRs were not serious (81.70%) in nature. However, 43 were serious in nature in which 16 required hospitalization, 17 required intervention to prevent permanent damage, and 10 were life threatening. The serious ADRs were reported more in ZLN (18%) regimen as compared to TLE (9%) ($P < 0.05$).

DISCUSSION

This study focused on the pattern of ADRs in different drug regimens used as ART at a tertiary care teaching hospital. ADRs were common in young age group with male predominance. On comparing two most commonly used regimens, TLE and ZLN, it was found that ADRs were more common and serious in nature with ZLN as compared to patients treated with TLE. The most common system organ involved in ZLN regimen was blood and skin while it was neurological and renal disorder in TLE regimen. The number of patients required withdrawal due to ADR was higher in ZLN as compared with TLE. In both regimens, majority of ADRs developed within the 7 days to 1 month of initiation therapy. A substantial number of ADRs were mild in severity and showed possible causal relation with ART.

Table 2: List of common adverse drug reactions according to system organ involved

Skin and appendage disorders (71)	Rash (50) SJ syndrome (11) Rash and itching (3) Blackening (nail/palm/sole) (2) Hyperpigmentation (face and tongue) (2) Facial eruption (1) Erythroderma (1) Vesicle (1)
Blood disorders (60)	Anemia (57) Pallor, weakness (3)
Neurological disorders (65)	Dizziness (35) Giddiness (8) Vertigo (6) Depression and suicidal tendency (2) Vivid dreams (2) Insomnia (5) Headache (5) Tingling (2)
Gastrointestinal disorders (32)	Nausea (10) Diarrhea (7) Gastric discomfort (6) Abdominal pain (3) Acute pancreatitis (1) Decrease appetite (1) Oral ulcer (4)
Renal disorders (31)	Raised serum creatinine levels (31)
Liver and biliary disorders (17)	Altered LFT (17)

SJ=Stevens-Johnson; LFT=Liver function tests

The reporting rate of ADRs due to ART was 10.89% in this study which is more as compared to the study done by Tadesse *et al*. where the mean number of ADR reported was 3.7%[13] It shows that clinician at our center is more aware in ADR reporting and this can also because of coordination between PvPI and the National AIDS Control Programme. In our study, males were more affected than females which is similar to other studies as shown in Table 3.[14-16] However, in other studies, females were commonly affected.[17] Possible explanation for this gender difference is because of the incidence of AIDS in male, hormonal effect on drug metabolism, body mass index, and genetic constitution.[16,18,19] In this study, ADRs were most commonly found in the age group of 38–48 years followed by 27–37 years. Almost similar results were found in the study of Agu and Oparah and Patel *et al*. where age group commonly involved was 30–44 and 31–45 years, respectively.[16,20] Maximum ADRs were seen in the reproductive age group because they comprised the major part of the study population.

In the present study, the most common systemic presentation included skin and appendage disorders followed by neurological disorders and blood disorders. While a study done by Patel *et al*.,

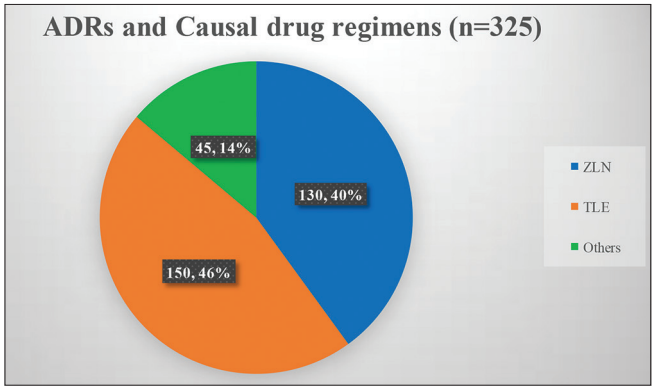

Figure 2: Causal drug regimens and adverse drug reactions. Others include atazanavir/ritonavir, nevirapine, co-trimoxazole, stavudine + lamivudine + nevirapine, lopinavir/ritonavir, abacavir, abacavir + lamivudine, abacavir + lamivudine + atazanavir/ritonavir, tenofovir + lamivudine + atazanavir, and zidovudine + lamivudine + lopinavir/ritonavir

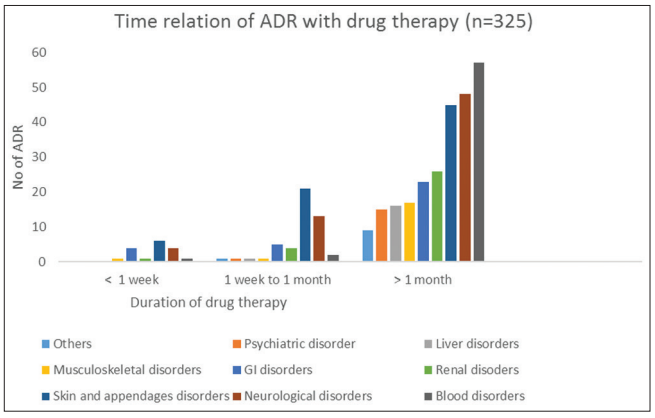

Figure 3: Time required for adverse drug reaction to occur after starting drug therapy. Others include metabolic and nutritional disorders and hearing and special sense disorders

Table 3: Comparison of our study with other similar studies

Parameters	Our study (2017)	Sadiq *et al*., 2016[15] Jammu and Kashmir	Patil *et al*., 2016[14] Maharashtra	Patel *et al*., 2015[16] Gujarat
Gender (%)				
Male	58.1	57	60.55	60.6
Female	41.8	43	39.45	39.3
Most common SOC (%)	Skin and appendage disorders (22) Neurological disorders (20) Blood disorders (18)	Not done	Not done	Gastrointestinal disorders (30.29) Cutaneous disorders (25.9) Neurological disorders (17.8)
Most common presentation (%)	Anemia (17.53) Rash (15.38) Dizziness (10.76)	Anemia (12) Gastritis (12) Vomiting (11.7)	Anemia (76.52) Skin rash (11.36) Increased LFT (6.06)	Papules (31) Pruritus (26) Nausea (23)
Most common drug causing ADR (%)	ZLN (69) TLE (14) Atazanavir/ritonavir (4)	ZLN (70.27) SLN (21.6) SLE (8.1)	ZLN (74.3) SLE/N (10.09) TLN/E (9.17)	ZLN (54) SLN (26) SLE (9)
Causality (%)				
WHO-UMC				
Possible	78.15	Not done	Not done	86.13
Probable	18.76			13.86
Naranjo score				
Possible	74.76	93.69	90.91	52.18
Probable	24.61	6.3	9.09	47.82
Severity (%)				
Mild	86.7	70.27		8.39
Moderate	4.9	27.02	68.9	88.69
Severe	8.3	1.78	30.3	2.92
Seriousness (%%)				
Serious	18.3	Not done	Not done	23.4
Not serious	81.7			76.64

ZLN=Zidovudine + lamivudine + nevirapine; ADR=Adverse drug reactions; TLE=Tenofovir + lamivudine+efavirenz; UMC=Uppsala Monitoring Centre; WHO=World Health Organization; SOC=System organ Classification

Jamnagar, showed that the most commonly affected systems are gastrointestinal disorders followed by cutaneous and neurological disorders[16] [Table 3], in a study by Tetteh *et al*., anemia is the most common systemic presentation (18.5%).[21] The most common ADR in our study is anemia followed by rash and dizziness. Similar to our study, in the study done by Patil *et al*. and Sadiq *et al*. also, anemia was the most common ADR[14,15] [Table 3].

ADRs were reported more frequently with ZLN as compared to patients treated with TLE. While in other studies, as shown in Table 3, the most common regimen responsible for ADRs are ZLN and SLN/E.[14-16] The reason for this can be due to drug regimens prescribed for HIV patients. We have seen less number of ADR with other regimen as TLE and ZLN are first-line regimens; if patients do not respond or developed some serious ADRs, then they are prescribed second-line regimens such as atazanavir/ritonavir + lamivudine + efavirenz and abacavir + lamivudine + atazanavir/ritonavir[6] [Table 3]. In our study, zidovudine-based regimen is most commonly associated with anemia, and efavirenz-based regimen (TLE) is associated with neurological disorders. Furthermore, we have seen good number cases of kidney injuries, and most of them are because of tenofovir which is known to cause renal toxicity.[22] These patients should be monitored by serum creatinine to prevent permanent renal damage.

Causality assessment using standard methods is one of the best ways to establish the causal relationship between a drug and adverse event. Furthermore, it is essential to determine whether drug discontinuation is mandatory as well as to put emphasis on patient education to avoid adverse event in future. In the present study on doing causality assessment using the Naranjo and WHO-UMC ADR causality scale, most of the ADRs were categorized as possible followed by probable in nature. This could be because most of the ART regimens are given in fixed-drug combinations, so it is difficult to pinpoint which drug has caused the reaction; also, HIV itself can present with these symptoms and polypharmacy is common. In few of cases, drugs were stopped, but because of spontaneous reporting, we are not able to follow-up; hence, majority of ADRs fall in category of "possible." Also most of the ADRs are affecting gastrointestinal tract and neurological which does not allowed stoppage of drugs and causality

assessment falls to possible in nature. Similar findings were observed by Patil *et al*., Sadiq *et al*., and Patel *et al*. [Table 3].[14-16] Majority of ADRs were mild in nature, and majority of ADRs in our study were not serious. Similar results were found in the study by Patel *et al*.[16] [Table 3]. ADRs developed were more serious with ZLN drug regimen compared to TLE regimen. This may be the reason as NACO recommends tenofovir-based regimen as first line.

Most of ADRs developed mostly after 1 month of taking suspected medication which included blood disorders, renal disorders, liver and biliary disorders, and neurological disorders. Few ADRs were also observed on starting therapy which includes skin and appendage disorders, gastrointestinal disorders, and neurological disorders. Similar results were found in a study by Patel *et al*. where also most of the ADRs developed between 1 and 6 months of initiation of therapy.[16] It shows that ADRs can developed any time during drug therapy, and hence, all the patients should be closely monitored for ADRs.

The limitations of the study are not able to calculate incidence rate, underreporting, lack of information about substituted drugs or treatment of ADRs, and single center. Furthermore, we have not done efficacy analysis as CD4 count and viral load details were not available.

CONCLUSION

Both ART regimens are associated with ADRs affecting all body system; however, the frequency and severity of ADR are high with ZLN regimen.

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Conflicts of interest

There are no conflicts of interest.

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