Original Article

A prospective study to estimate the incidence and pattern of adverse drug reactions to first-line antiretroviral therapy (tenofovir, efavirenz, and lamivudine)

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Abstract

Background: Antiretroviral drugs are efficacious but are associated with long-term toxicities, drug interactions, and emergence of drug resistance. **Objective:** To study the incidence and pattern of adverse drug reactions in human immunodeficiency virus (HIV) patients receiving first-line antiretroviral therapy (ART) (tenofovir, efavirenz, and lamivudine (TEL) which was introduced by NACO in 2013. **Materials and Methods:** A prospective, single-center observational study that included 135 treatment-naive HIV patients who were started on fixed drug once-daily regimen (TEL). At baseline, detailed clinical history, body weight, waist–hip ratio, complete blood count, liver and renal function test, CD4 cell count were performed. Clinical monitoring for cutaneous, neuropsychiatric, and gastrointestinal side effects was done every month along with laboratory monitoring and anthropometric measurement for every 6 months. CD4 counts were measured at baseline and end of the study at 12 months. **Results:** Out of 135 participants, 89 (65.9%) were males and 46 (34%) were females. The mean age and the mean duration of illness at inclusion were 35.10 ± 8.97 years and 1.2 ± 0.6 years, respectively. The mean increase in weight at baseline and at 12 months (57.55 ± 6.56 to 64.04 ± 8.2) was statistically significant (95% confidence interval [CI]: 4.35–8.62, $P < 0.001$). The mean CD4 counts at baseline were 309.73 ± 118.44 and increased after 12 months of treatment to 421 ± 129.4 which was statistically significant (95% CI: 81.54–140.99, $P < 0.001$). The mean difference in platelet count was statistically significant between baseline and 12 months (95% CI: 10.32–46.13, $P = 0.002$). The mean difference in serum urea levels at baseline and at 6 months (95% CI: 0.60–1.61, $P < 0.001$) as well as 12 months were statistically significant (95% CI: 0.08–1.03, $P = 0.02$). The mean increase in serum creatinine at baseline (0.75 ± 0.12) and at 12 months (0.97 ± 0.16) was also significant (95% CI: 0.21–0.28, $P < 0.001$). There was a significant difference between mean creatinine clearance at baseline and at 12 months (109.9 ± 13.75 to 99.33 ± 12.52, $P < 0.0001$). One patient discontinued treatment due to adverse effects while two patients were shifted to second-line antiretroviral treatment. **Limitations:** Small sample size, single-center study and short follow-up period, long-term toxicities were not appreciated. **Conclusion:** Fixed drug combination with TEL as a first-line ART for HIV is a safe regime as we observed minimal side effects with current regimen.

Key words: Adverse drug reactions, antiretroviral therapy, efavirenz, first line, highly active antiretroviral therapy, human immunodeficiency virus, lamivudine, tenofovir

Introduction

It is estimated that around 38 million people are currently living with human immunodeficiency virus (HIV) at the end of 2019 in the world. Among which, 25.4 million are receiving antiretroviral treatment.[1] In India, estimated number of people living with HIV are 23.48 lakh at the end of 2019.[2] The standard treatment consists of combination of at least three drugs (called highly active antiretroviral therapy [HAART]) that suppress HIV replication. HAART has led to a significant reduction in

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AIDS-related mortality and morbidity and has transformed HIV infection into a manageable chronic condition as well as preventing HIV transmission. Although ART does not cure HIV/AIDS, it inhibits the efficient replication of the HIV virus, and reduces viremia to undetectable levels. The first drug that was effective against HIV, zidovudine (ZDV) was approved as early as 1986. Until the early nineties, only zidovudine (ZDV) and didanosine were available and used as monotherapy. In 1996 protease inhibitors were introduced, which were very potent drugs and reduced the viral load by 10–100 times. These drugs were quite efficacious but were associated with problems of significant toxicities, adherence to large number of pills (20–30 per day), and high costs.[3] Earlier zidovudine (ZDV)/stavudine (d4T), lamivudine (3TC), nevirapine (NVP)-based regimens were used as a component of HAART. Use of these drugs as a first-line therapy has now been stopped and replaced by tenofovir disoproxil fumarate (TDF)/3TC/efavirenz (EFV) due to similar potency, lesser expense, lower side effect profile, and lower prevalence of primary resistance in the population.[4]

The WHO proposed to test and treat all new HIV-positive patients and NACO is planning to change the CD4 limit of initiating the treatment from 350 to 500.[5] This would mean that the patient will be started on ART earlier and continue for long term, thus predisposing the patients for drug toxicities and may be more morbidity. In the current scenario, we require a safe regimen which can be given for long duration. This study has provided the information on the rate of known side effects and occurrence of rare adverse drug reactions (ADRs) and this information will be used for treatment guidelines review, pharmaceutical planning, and decision-making regarding the new regimen.

Materials and Methods

This was a single-center, prospective study undertaken at our institute from July 2016 to December 2017. The study protocol was approved by the institute's Ethics Committee. All ART naive HIV patients >18 years of age, who were to be initiated on first-line ART and willing for follow-up visits as per protocol were recruited after obtaining written informed consent. Pregnant and lactating patients, elderly patients aged 70 years or older, patients with diabetes and hypertension, and patients unwilling to give informed consent were excluded. At baseline, detailed clinical history, clinical evaluation, body weight, waist–hip ratio, complete blood count (CBC), liver function test, renal function test, and CD4 cell count were performed. Clinical monitoring for cutaneous, neuropsychiatric, and gastrointestinal (GI) side effects was done every month while laboratory monitoring along with anthropometry measurement was done at the interval of every 6 months till 12 months. CD4 counts were measured at baseline and end of the study i.e., at 12 months.

Statistical analysis

The statistical analysis was carried out using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Univariate analysis was used for comparison of qualitative outcomes such as gender. Age-wise comparison was performed for all clinical parameters (CBC, lipid profile, etc.) either by using parametric independent Student's *t*-test (or its nonparametric Mann–Whitney *U* test). Association of categorical risk factors was assessed using Chi-square test or Fisher's exact test whichever applicable. All statistical tests were two-tailed and $P < 0.05$ was taken as significant.

RESULTS

The patients from the ART center of our hospital were screened over a period of 6 months and 135 patients were recruited. All the patients were ART naive and started on once daily fixed drug combination of TDF/3TC/EFV. Three monthly follow-up assessments were carried out after baseline assessment. Three patients after first visit and eight patients after 6 months didn't come for follow-up visits despite several reminders.

Unprotected sexual contact was the most common route of transmission (94.3% for male patients and 95.65% for female patients) followed by needle stick injury (2.33% in males and 4.34% in females) and blood transfusion (3.37% in male patients).

Baseline demographic characteristics studied including age at the time of inclusion, history of smoking, alcohol consumption, sexual preferences, route of transmission for HIV, weight, height, and waist–hip ratio are illustrated in Table 1. There was a significant increase in weight (kg) from 57.55 ± 9.56 at baseline to 61.04 ± 8.2 at 12 months ($P = 0.001$).

Out of 135 patients, Grade 1 skin rash was seen in 11 (8.15%) while Grade 2 rash was noted in one patient (0.74%) illustrated in Table 2. Patients with Grade 1

Table 1: Baseline demographic details of the study cohort

Demographic characteristics	Mean/*n* (%)	*P*	95% CI
Age at inclusion (years)	35.10±8.97		
Sex			
Male	89		
Female	46		
Height (cm)	162.29±7.92		
Weight (kg)			
At baseline (males)	57.55±9.56	0.07	−0.22-4.08
6 months	59.48±8.39		
At baseline (females)	57.55±9.56	<0.001	4.35-8.62
12 months	64.04±8.2		
Alcoholic			
Male	9 (10.47)		
Female	0		
Smoker			
Male	17 (19.77)		
Female	0		
Waist-hip ratio			
At baseline (males)	0.82±0.05	1.0	−0.01-0.01
6 months	0.82±0.05		
At baseline (females)	0.82±0.05	0.1	−0.002-0.02
12 months	0.83±0.05		
Sexual preferences			
Heterosexual	128 (94.8)		
Homosexual	7 (5.2)		
Route of transmission			
Blood transfusion			
Male	3/89 (3.37)		
Female	0/46		
Sexual contact			
Male	84/89 (94.3)		
Female	44/46 (95.65)		
Needle stick injury			
Male	2/89 (2.24)		
Female	2/46 (4.34)		

CI=Confidence interval

Table 2: Dermatological adverse effects after the start of antiretroviral treatment

severity grade	clinical features	Males, *n* (%)	Females, *n* (%)
Grade 1 rash	Erythema, pruritus	4 (2.96)	7 (5.19)
Grade 2 rash	Diffuse maculopapular rash, dry desquamation	0	1 (0.74)
Grade 3 rash	Vesiculation, moist desquamation, ulceration	0	0
Grade 4 rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis	0	0
Treatment discontinuation as a result of rash	DRESS	1 (0.74)	0

DRESS=Drug rash with eosinophilia and systemic symptoms

rash were treated with oral antihistamines and emollients along with ART discontinuation. In these patients, skin lesions resolved within 1 week. One patient presented with rash after 5 weeks of starting ART which was diagnosed as drug hypersensitivity syndrome, so tenofovir, efavirenz, and lamivudine (TEL) regimen was discontinued and he was started started on alternative regimen (Ritonavir, Tenofovir, and 3TC).

Neuropsychiatric symptoms [Table 3] such as insomnia, nightmares, vertigo, dizziness, and anxiety were seen in 38 (28.15%) patients, among those, 23 (17.04%) were males and 15 (11.11%) were females. These symptoms started within 1st or 2nd day of therapy and resolved after 2–4 weeks of therapy. There was no change in mini mental status as it remained the same throughout the study period of 1 year.

GI symptoms [Table 4] such as gastritis, loss of appetite, diarrhea, and nausea were seen in 32 (23.7%) patients of total 135 patients. GI symptoms mainly occurred within 1–2 weeks of initiation of ART which subsided in 4 weeks. None of the patients with neuropsychiatric and GI symptoms require discontinuation of ART.

There was a mean improvement in CD4 count from 309.73 ± 118.44 at baseline to 421 ± 129.4 at 12 months, which was also statistically significant ($P < 0.001$). The change in platelet count was also statistically significant between baseline was 283.17 ± 78.45 × 10^3 and at 12 months it was 311.40 ± 70.79 ($P = 0.002$), though clinically insignificant mild increase in serum urea (mg/dl) levels was observed from 30.56 ± 2.07 at baseline to 31.67 ± 2.17 at 6 months and 31.12 ± 1.86 at 12 months ($P = 0.02$)., Increase in the serum creatinine at the end of the study was statistically significant (0.72 ± 0.12 to 0.97 ± 0.16, $P < 0.0001$) though clinically insignificant. There was a significant difference between mean creatinine clearance at baseline and at 12 months (109.9 ± 13.75 to 99.33 ± 12.52, $P < 0.0001$). All the laboratory parameters are illustrated in Table 5. There was no significant alteration in the other laboratory parameters observed.

Table 3: Neuropsychiatric symptoms after the start of antiretroviral treatment

Symptoms	Males, *n* (%)	Females, *n* (%)
Insomnia	4 (2.96)	2 (1.48)
Suicidal tendency	0	0
Hallucination	0	0
Nightmares	5 (3.7)	2 (1.48)
Vertigo	11 (8.15)	6 (4.44)
Headache	0	0
Dizziness	2 (1.48)	3 (2.22)
Anxiety	1 (0.74)	2 (1.48)
Total	23 (17.04)	15 (11.11)

Table 4: Gastrointestinal symptoms

Symptoms	Males, *n* (%)	Females, *n* (%)
Gastritis	3 (2.22)	5 (3.7)
Loss of appetite	6 (4.44)	3 (2.22)
Diarrhea	3 (2.22)	1 (0.74)
Nausea	5 (3.7)	6 (4.44)
Vomiting	0	0
Abdominal pain	0	0
Total	17 (12.59)	15 (11.11)

Discussion

In this prospective study, we tried to estimate the incidence and pattern of ADR to new first-line ART (TDF/3TC/EFV) over a period of 12 months. Unprotected sexual contact was the most common route of transmission in 94.3% for male patients and 95.65% for female patients followed by needle stick injury (2.33% in males and 4.34% in females) and blood transfusion (3.37% in male patients). According to NACO, maximum chances of the transmission of infection are through unprotected sexual contacts followed by injectable drug abuse and then blood and blood products.[6]

In our study 60.74% of patients presented with ADRs which were mostly during the first 12–16 weeks of treatment. Incidence of ADRs was seen more in males which is consistent with a study by Jha *et al.*, however, the regimen used by them was zidovudine, NVP, and EFV based.[7] In our study, the most frequent adverse events seen were neuropsychiatric, GI followed by dermatological side effects. In a study by Jha *et al.*, the most common adverse effect was dermatological, followed by hepatic, hematological, neurological, and gastrointestinal.[7] This can be explained by the fact that the regimen used in a later study was zidovudine based.

Minor neuropsychiatric side effects were reported by 28.15% of patients. These symptoms usually began during the 1st or 2nd day of therapy and resolved after the 2 to 4 weeks of therapy. Dizziness, insomnia, vertigo, and vivid dreams were the most frequently reported neuropsychiatric adverse events. In a study by Mollan *et al.*, they compared time to suicidality and neuropsychiatric adverse effects with EFV combining with other antiretroviral drugs versus EFV-free antiretroviral regimens for the treatment of HIV, however we did not observe such severe neuropsychiatric adverse events in our cohort.[8] In contrast to a study by Mollan *et al.*,[8] neuropsychiatric adverse events were more in males and also side effects such as suicidal tendencies, depression, or aggressive behavior were not seen in any of our patients. There was no change in mini mental status as it remained same throughout the study period of 1 year. None of the patients discontinued therapy because of neuropsychiatric symptoms.

Table 5: Laboratory findings

Variables	Baseline	6 months	*P*	95% CI	12 months	*P*	95% CI
CD4 count	309.73±118.44				421±129.4	<0.001	81.54-140.99
Hemoglobin	11.71±2.03	11.83±1.86	0.61	−0.34-0.58	12.07±1.86	0.12	−0.10-0.82
TLC	6169.19±3162.02	6044.3±2038.37	0.70	−762.38-512.60	5832.74±1661.3	0.27	−941.71-268.81
Platelet count	283.17±78.45	297.81±65.81	0.09	−2.71-31.99	311.40±70.79	0.002	10.32-46.13
Total serum bilirubin	1.16±1.72	1.05±1.52	0.58	−0.49-0.27	0.88±0.92	0.09	−0.61-0.05
SGOT	42.36±52.22	39.53±34.66	0.60	−13.45-7.79	36.15±22.08	0.20	−15.81-3.39
SGPT	35.5±37.93	33.62±27.78	0.64	−9.84-6.08	33.90±24.61	0.68	−9.26-6.06
Serum urea	30.56±2.07	31.67±2.17	<0.001	0.60-1.61	31.12±1.86	0.02	0.08-1.03
Creatinine	0.72±0.12	0.75±0.12	0.04	0.001-0.05	0.97±0.16	<0.001	0.21-0.28
Creatinine clearance	109.8±14.59	109.9±13.75	0.95	−3.29-3.49	99.33±12.52	<0.001	−13.72-−7.21
Triglyceride	111.34±24.58	112.51±23.62	0.68	−4.60-6.94	113.67±23	0.42	−3.37-8.03
LDL	101.34±22.44	97.25±19.3	0.10	−9.10-0.92	97.64±20.32	0.97	−8.82-1.42
HDL	46.21±7.04	48.53±25.98	0.35	−2.42-6.70	47.79±6.58	0.06	−0.05-3.21

TLC=Total leucocyte count; SGOT=Serum glutamic oxaloacetic transaminase; SGPT=Serum glutamate pyruvate transaminase; LDL=Low-density lipoprotein; HDL=High-density lipoprotein; CI=Confidence interval

Transient GI symptoms were the second most frequent side effects reported by 23.7% of patients in this study which was comparable to the study by Jena *et al*.[9] GI side effects occurred in 1–2 weeks of initiation of ART and then subsided after 4 weeks. Patients most commonly had loss appetite, nausea, vomiting, and diarrhea. However, in a study by Kathwate and Shah, the adverse effect profile of tenofovir-based regimen in children, with 3TC and EFV as the other drugs was studied, and no adverse effect or failure of treatment was noted, indicating that TEL has good GI safety profile in HIV-infected children.[10]

In our study, skin rash was seen in 13 (9.6%) patients, almost similar results were seen in a study by Manosuthi *et al.*, where 8.2% of patients developed skin rash. They included 122 patients who had preceding NVP-associated rash, and then shifted them to EFV based regimen, only 8.2% developed skin rash, thus signifying that EFV is associated with less incidence of rash compared to NVP-based regimens.[11] In our study, rash appeared in 4–12 weeks of initiation of ART. Grade 1 skin rash was most frequently seen in the form of erythema, pruritus, and urticaria which resolved with antihistamines and emollients and did not require discontinuation of ART. The incidence of rash in females (5.93%) was twice in comparison to males (2.96%) which was consistent with a study previously conducted by Sarfo *et al*.[12] In a study by Sarfo *et al*., they concluded people with NVP-based therapy were more likely to develop Grade 3 and 4 rash and had 11 times more chances of discontinuing therapy due to rash.[12] In our study, only one patient discontinued therapy due to development of drug rash with eosinophilia and systemic symptoms or drug hypersensitivity syndrome and none of our patients developed Grade 3 and Grade 4 rash.

Akinboro *et al*. studied the effect of zidovudine, 3TC, and either of NVP or EFV on weight and body mass index. They found a progressive increase in weight with a mean increase of 6.16 ± 0.54 kg in the patients on ART.[13] Similar results were observed in our set of patients i.e., a mean increase in weight of 6.49 ± 1.56 kg. So, both the regimens showed progressive weight gain at the end of 1 year of study. However, a study by Gallant *et al*. observed a decrease in the weight after 6 months of the ART with d4T-based regimen and maintained weight gain with tenofovir-based regimen even after 36 months with 3TC and EFV as the other drugs.[14] This may be explained by progressive lipoatrophy as a major adverse effect of d4T therapy. There was a progressive increase in mean waist–hip ratio of patients at all the follow-ups but the difference was not statistically significant.

The mean CD4 count of the patients at 12 months of study period was increased in comparison to baseline (309.73 ± 118.44 to 421 ± 129.4) and the difference was statistically significant, as found in earlier studies.[13] In our patients, anemia was mostly seen in patients with comorbid conditions such as tuberculosis and viral hepatitis. There was a slight increase in hemoglobin levels at 6 months and at 12 months but the difference was not statistically significant. We did not observe any significant changes in the hemogram and other parameters such as TLC, however, platelet counts were significantly decreased at 12 months (but were not <100,000/ul).

Transaminase levels improved during therapy which was clinically significant but not statistically significant. Wu *et al*., in their study done on HIV with hepatitis C virus (HCV)/hepatitis B virus co-infection patients, found similar findings.[15] However, in a study done by Ankur Jain *et al*., the mean serum glutamic oxaloacetic transaminase of patients decreased gradually between baseline at 6 months and at 12 months while mean serum glutamate pyruvate transaminase remained approximately same throughout the study period of 12 months. Patients with concomitant viral hepatitis had transaminitis (up to 5 times the upper limit) at baseline and the same were treated with anti-HCV drugs. In hepatitis B surface antigen-positive patients, TEL regimen was only given to cover both HIV and hepatitis B. None of the patients had concomitant hepatitis B and hepatitis C infection.[16]

Pujari *et al*. observed that 2.8% of patients on TDF/FTC/EFV developed renal toxicity.[17] We did not observe any nephrotoxicity in our patients due to lesser mean age and short follow-up period, however, we observed an increase in both urea and creatinine at 6 months and 12 months, clinically nonsignificant but statistically significant. There was no significant difference in mean creatinine clearance at baseline and at 6 months, however, a significant difference was observed between baseline and at 12 months. Thus, an increase in serum creatinine and fall in creatinine clearance but although it was within normal range but may also indicate early renal injury.

In a study by Moyle *et al*., 79 out of 157 patients receiving study drug (ABC/3TC + EFV) were switched to EFV/

FTC/TDF, leading to significant improvement in lipid parameters.[18] We did not observe any dyslipidemia in any of our patients during the study period.

Side effect profile of previous versus current antiretroviral therapy regimen

Zidovudine has been associated with higher short-term hematological, GI, and long-term metabolic and morphological toxicities.[19,20] d4T is associated with long-term toxicities including lactic acidosis, pancreatitis, hyperlipidemia, lipoatrophy, and peripheral neuropathy which are often irreversible.[21] The incidence of pulmonary tuberculosis has risen in HIV patients in the recent past, making EFV a preferred drug when concomitant use of rifampicin is indicated, however, the major side effect of EFV is neurological and cutaneous, thus NVP being the preferred drug for patients with underlying psychiatric illness.[22] Tenofovir has been rarely associated with renal toxicity and bony side effects. 3TC is the preferred backbone as it has the lowest toxicity profile among all drugs.[4]

Limitations

Smaller sample size and inability to appreciate long-term side effects of ART such as peripheral neuropathy, lactic acidosis, dyslipidemia, or cardiovascular disease, because of short follow-up period of 1 year were major limitations of our study.

Conclusion

To conclude this fixed drug combination (TEL) as a first-line ART for HIV is a safe regime as we observed minimal side effects in the form of neuropsychiatric, GI, dermatological, nephrotoxic, and hematological adverse events.

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Conflicts of interest

There are no conflicts of interest.

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