Original Article

Tenofovir-based first-line regimen in newly diagnosed HIV-patients: An experience from a Tertiary Care Hospital in India

Arkapal Bandyopadhyay, Sarika Palepu[1], Bhawna Saini, Rakesh Chandra Chaurasia[2], Rakesh Kumar Yadav[3]
Department of Pharmacology, All India Institute of Medical Sciences, Rishikesh, [1]Department of Community Medicine, VCSGGMS & RI, Srinagar, Uttarakhand, Departments of [2]Pharmacology and [3]Internal Medicine, Moti Lal Nehru Medical College, Allahabad, Uttar Pradesh, India

Address for correspondence:
Dr. Sarika Palepu, Department of Community Medicine, VCSGGMS & RI, Srinagar - 246 174, Uttarakhand, India.
E-mail: sarikapalepu@gmail.com

Abstract

Introduction: India has a huge burden of HIV/AIDS infection. Tenofovir-based first-line therapy is the preferred treatment for newly diagnosed cases of HIV infection. **Materials and Methods:** The present prospective study was done among newly diagnosed cases of HIV infection. The patients were followed up for 6 months from the day of enrollment. Sociodemographic parameters, CD4 counts, and adverse drug reactions (ADRs) were analyzed at baseline and after 6 months. Bivariate and multivariate logistic regression was performed with the occurrence of ADRs as outcome variable. **Results:** In this study, 67 patients were enrolled with a mean age of 32.75 (±14.39) years. Mean CD4 count at the start of treatment was 241.5/mm^3. The mean difference in CD4 count was 383.05/mm^3 (standard deviation = 274.9). Dizziness, tingling, numbness of extremities, and muscle cramps were the most common adverse effects. On multivariate logistic regression, the occurrence of ADRs was seen to be significantly higher only in illiterate patients. **Conclusion:** The present study highlights the importance of long-term follow-up of the patients on antiretroviral therapy. Adequate monitoring of the treatment parameters is of utmost importance.

Key words: Adverse drug reactions, antiretroviral therapy, HIV, tenofovir

Introduction

Globally, about 37.9 million (32.7–44.0 million) people were living with HIV in 2018. An estimated 0.8% (0.6%–0.9%) of adults aged 15–49 years are living with HIV/AIDS worldwide. In 2018, about 1.7 million people were infected with HIV/AIDS indicating that the continuous burden of the disease is a global concern.[1] In India, the burden of HIV/AIDS is constant in recent times. As per India HIV Estimation 2017 report, the prevalence among adults of 15–49 years is estimated at 0.22% (0.16%–0.30%) in 2017. The adult HIV prevalence in India had its steady decline from 0.38% in 2001 to 0.34% in 2007, 0.28% in 2012, and 0.26% in 2015 to 0.22% in 2017.[2]

Highly active antiretroviral therapy forms the cornerstone of the treatment of HIV infection.Tenofovir disoproxil fumarate + lamivudine (3TC) + efavirenz (EFV) combination was the preferred first-line ART regimen for adults and adolescents according to the WHO.[3,4] It has been implemented in India by the National AIDS Control Organization (NACO). Tenofovir disoproxil is a nucleotide analog reverse-transcriptase inhibitor. Lamivudine, a nucleoside analog, is a potent reverse-transcriptase inhibitor. EFV is classified as a nonnucleoside reverse-transcriptase inhibitor. Once daily tenofovir-based first-line regimen has better compliance and has improved adverse drug reaction (ADR) profile as compared to zidovudine- or stavudine-based therapy.

The objectives of the present study were to assess ADRs in patients newly receiving TLE regimens in a tertiary care hospital at Allahabad, Uttar Pradesh, and also to study the association between selected variables and the occurrence of ADRs.

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Materials and Methods

The present study was conducted in an ART Centre associated with Moti Lal Nehru Medical College, Allahabad. All patients who were registered in the ART center over 3 months of study duration, started on TLE regimen, who were willing to participate, and gave written informed consent were included in the study. Participants who were seriously ill, suffering from psychiatric disorders and who could not comprehend interview questions were excluded from the study. A written informed consent was taken from the patient and an attendant in a local language (Hindi). Assent was taken from parents/caregivers of participants who were below 18 years of age.

The prospective cohort of patients was given tenofovir-based first-line therapy with tenofovir (300 mg), lamivudine (200 mg), and EFV (600 mg) (TLE) one tablet, once daily as a standard regimen approved by the WHO and implemented by the NACO. The patients were observed for a period of 6 months from the date of enrollment and followed up on monthly basis. The drugs were dispensed free of cost from the ART center of the institute. CD4 count was done as per the standard guidelines. Patients with other concomitant comordities were advised to continue their treatment as advised by the treating physician.

Sociodemographic profile, associated comorbidities, and baseline CD4 counts were documented in a pretested semi-structured questionnaire. Patients were counseled by designated persons regarding the disease process, treatment, and adverse events associated with therapy in the ART center.

During recruitment, the patient registration card issued by the hospital as per NACO guidelines was thoroughly checked for CD4 counts, changes in regimen, and any adverse reactions. Each study participant was then given a card containing a unique identification code, date of follow-up visit, and the investigator's contact number to contact if there is any emergency during or after the study period. All norms of confidentiality were strictly maintained and followed. During the follow-up period, in every patient with a suspected adverse event, a detailed drug history including drugs used during the 3 weeks preceding the adverse reaction, route of administration, dosage, concomitant medical products if any including self-medication and herbal remedies, duration of treatment, improvement after discontinuation of drug, purpose of taking the drug, whether prescribed or over-the-counter drug was noted. A detailed drug reaction history was noted. Grading of the ADRs was done according to standard guidelines of the WHO. The WHO-ADR probability scale and Naranjo's algorithm were used for the causality assessment of the ADRs. The severity of the ADR was assessed by the Modified Hartwig and Siegel Scale. The preventability of ADR was assessed by the Modified Shummock and Thornton Scale.

In this study, ADR is defined as any response to a drug which is noxious and unintended, and which occurs at doses normally used in human beings. Poor adherence was defined as missing at least one pill in the past week by the patients.

Data were collected and analyzed in StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Normality test was carried out on all continuous variables and presented as either mean ± standard deviation (SD). Bivariate logistic regression was done to assess the occurrence of ADRs with selected variables using Chi-square test. Variables which were found to be significant (at $P < 0.25$) were considered for inclusion in multivariate analysis. Multivariate logistic regression was performed with the outcome variable as the occurrence of ADR (coded as binary). Variables with $P < 0.05$ on multivariate logistic regression were considered significant. The study was approved by the institute ethics committee.

Results

About 70 patients were started on TLE regimen during the study period. Three patients refused to participate and 67 were included in the study.

The age of the patients showed a wide variation ranging from 3 to 65 years. Among the study participants, 53.7% were females, 41.8% were illiterates, 73.1% were married and 44.7% were either unemployed or students. The mean monthly income of the patients was 2321 rupees. It was seen that the majority of the patients belonged to nuclear family (85%) with no history of migration (86.6%) [Table 1].

Table 1: Sociodemographic characteristics of patients on tenofovir lamivudine efavirenz regimen

Characteristic	Results, *n* (%)
Age (years), mean±SD	3-65 (32.75±14.39)
Gender	
Males	31 (46.3)
Females	36 (53.7)
Education	
Illiterate	28 (41.8)
Primary school completed	8 (11.9)
Middle school completed	14 (20.9)
High school completed	9 (13.4)
Graduate	2 (3.0)
Postgraduate	6 (9.0)
Marital status	
Married	49 (73.1)
Unmarried	6 (9.0)
Divorced	1 (1.5)
Widow/widower	1 (1.5)
Separated	10 (14.9)
Occupation	
Professional/semiprofessional	4 (6)
Clerk/shopkeeper/farmer	2 (3)
Skilled	4 (6)
Semiskilled	7 (10.4)
Unskilled	18 (26.9)
Unemployed/student	30 (44.7)
Home-maker	2 (3)
Mean monthly income (rupees) (range)	2321 (0-15,000)
Family type	
Nuclear	57 (85)
Extended	10 (15)
History of migration	
Yes	9 (13.4)
No	58 (86.6)
High-risk behavior	
Yes	65 (97)
No	2 (3)
Delay in treatment start (days), mean±SD (range)	143.2±493.05 (0-2900)
CD4 count, mean (range)	241.5 (32-496/mm^3)

SD=Standard deviation

High-risk behavior was seen in most of the patients (97%). History of other comordities was present in only two patients (11%). The mean delay in the start of treatment was very high corresponding to 143.2 days. The mean CD4 count of the patients was low at the start of the treatment (241.5) [Table 1].

The mean difference in the CD4 count from the start and 6 months of treatment was available for 51 patients. CD4 values deteriorated in 21 patients (range from − 8 to − 407) and improved in 30 patients. The mean difference in CD4 count was 383.05 (SD = 274.9).

At the end of 6 months of treatment with TLE regimen, health condition has improved in 65 patients (97%). Advice regarding ADRs was given in 64 patients (95.5%) and 65 patients were aware of any ADRs (97%). ADRs to ART regimen were seen in 38 patients (56.7%). About 165 ADRs were observed in the patients (range: 1–10) [Table 2].

Most of the ADRs were seen in males (n = 23, 60.5%). Majority of the ADRs were seen in patients of 15–45 years (n = 26, 68.5%), followed by 46–60 years (n = 9, 23.7%), <15 years (n = 2, 5.2%), and >60 years (n = 1, 2.6%).

The majority of ADRs were of central nervous system (46.1%), followed by musculoskeletal (18.2%) and gastrointestinal (17.6%). The most common ADR of central nervous system was dizziness (n = 18), followed by tingling and numbness (n = 15) in the extremities, headache (n = 11), insomnia (n = 11), depressive symptoms (n = 9), drowsiness (n = 5), vertigo (n = 3), anxiety (n = 2), and somnolence (n = 2). The most common ADR of musculoskeletal system was painful muscle cramps (n = 23), followed by weakness (n = 15). The most common ADR of gastrointestinal system was anorexia (n = 11), followed by increased appetite (n = 9), flatulence (n = 7), diarrhea (n = 4), and gastritis (n = 4). The most common ADR of skin was maculopapular skin rashes (8), followed by itching (5). Neutropenia (n = 7) was the common laboratory abnormality seen in patients [Table 3].

The causality assessment done by the WHO-UMC scale showed that 1.9% ADRs were certain, 38.4% ADRs were probable/Likely, 58.0% ADRs were possible, and 1.7% ADRs were Unlikely. When causality assessment was done by Naranjo's algorithm, 2.2% ADRs were definite, 36.4% were probable, and 61.4% were possible. Severity Assessment done by Modified Hartwig and Siegel Scale showed 56.4% of ADRs were of mild severity, 39.9% ADRs was of moderate severity, and 3.7% ADRs were of severe nature. Preventability assessment done by Modified Shummock and Thornton scale showed that ADRs were definitely preventable in 10.4% of patients, probably preventable in 76.4% of patients, and not preventable in 13.2% of patients. It was seen that 22 patients (32.8%) were nonadherent to treatment during the study course.

Bivariate logistic regression was done to assess the occurrence of ADRs with selected variables. It was seen that the occurrence of ADRs was more in males, illiterate patients, and those who were currently not working. However, on multivariate logistic regression, the occurrence of ADRs was seen to be significantly higher only in illiterate patients [Table 4].

Table 2: Adverse drug reactions in patients on tenofovir lamivudine efavirenz regimen

Number of ADRs	*n* (%)
0	29 (43.3)
1	7 (10.4)
2	6 (9)
3	5 (7.5)
4	3 (4.4)
5	6 (9)
6	1 (1.5)
7	4 (6)
8	1 (1.5)
9	3 (4.4)
10	2 (3)

ADRs=Adverse drug reactions

Table 3: System-wise adverse drug reactions among patients on tenofovir lamivudine efavirenz regimen

System involved	*n* (%)
Central nervous system	76 (46.1)
Musculoskeletal system	30 (18.2)
Gastrointestinal system	29 (17.6)
Skin	15 (9.1)
Laboratory abnormalities	9 (5.4)
Miscellaneous	5 (3.0)
Cardiovascular system	1 (0.6)
Total	165 (100)

Table 4: Association of adverse drug reactions with select sociodemographic variables

Variable	Un AOR; *P* (95% CI)	AOR; *P* (95% CI)
Age	1.01; 0.41 (0.97-1.06)	-
Gender		
Male	1	1
Female	0.25; 0.00 (0.08-0.70)	0.49; 0.26 (0.14-1.70)
Education		
Illiterate	1	1
Literate	0.19; 0.00 (0.06-0.57)	0.23; 0.01 (0.07-0.75)
Occupation		
Not working	1	1
Working	0.29; 0.01 (0.10-0.81)	0.44; 0.18 (0.12-1.49)
Family type		
Nuclear	1	-
Extended	1.17; 0.82 (0.29-4.60)	
History of migration		
Yes	1	-
No	1.77; 0.42 (0.43-7.28)	
Delay in treatment start		
No	1	-
Yes	1.56; 0.37 (0.57-4.21)	
CD4 count		
<250	1	-
≥250	1.27; 0.62 (0.48-3.38)	

OR=Odds ratio; CI=Confidence interval; Un AOR = Unadjusted Odds Ratio; AOR=Adjusted OR

Discussion

The present study evaluated the occurrence of ADRs to tenofovir-based first-line ART regimen among patients attending a tertiary care hospital in Allahabad.

In the present study, 53% were females. In a study by Chowta *et al*., it was observed that 53.8% were females among patients on tenofovir regimen, similar to our

study.[5] In the present study, it was seen that there was a wide range of delay in the start of treatment (mean days of 143.2 [±493.05] with range from 0 to 2900 days). Majority of the patients were illiterate and were either students/unemployed with a meager income. These factors might have affected treatment-seeking behavior. However, factors leading to the treatment delay in PLHIV should be assessed in greater detail from patient's and health system's perspective. Necessary remedial measures should be implemented to ensure early treatment initiation.

The mean CD4 counts of the patients at the start of ART were 241.5 cells/mm^3 in our study. In a study by Samar *et al*.,[6] CD4 counts of majority of the patients on TLE regimen ranged between 201 and 350 cells/mm^3 similar to our study. It was also seen that the mean difference in CD4 values deteriorated in twenty one patients (range from −8 to −407) and improved in thirty one patients in the present study. Reasons behind the deterioration in CD4 count was not analyzed in the study participants.

In the present study, no ADRs were observed in 42.1% of patients. Majority of the ADRs were among males and were in the age group of 15–45 years. In a study by Hemasri *et al*.,[7] no ADRs were seen in 42.18% of patients on TLE regimen similar to our study. In the present study, majority of the ADRs belonged to central nervous, musculoskeletal, and gastrointestinal system. In a study by Chauhan *et al*.,[8] 42% of the ADRs belonged to the central nervous system similar to our study. In a study by Joseph Andis *et al*.,[9] similar findings were seen as fatigue, headache, nausea, and vomiting were the most common ADRs. In a study by Samar *et al*.,[4] the majority of the ADRs were of neuropsychiatric manifestations similar to our study.

The causality assessment by the WHO-UMC scale showed that 58.0% of ADRs were possible. However, in a study by Chauhan *et al*.,[8] 83% of ADRs on TLE regimen were categorized as possible. By Naranjo's algorithm, 61.4% of ADRs were possible in our study. Severity assessment done by Modified Hartwig and Siegel Scale showed 3.7% ADRs were of severe nature unlike 9% of ADRs in TLE regimen as severe by Chauhan *et al*.[8]

To the best of our knowledge, the current prospective study is the first of its kind in Uttar Pradesh exclusively assessing the ADRs due to first-line ART regimen in PLHIV.

Conclusion

HIV/AIDS, a disease of global concern is widely prevalent. PLHIV have to take ART throughout their life to overcome the effects of HIV/AIDS. Hence, analyzing ADRs to ART regimens, first-line regimens in particular forms a mainstay of treatment course. Multitude of factors plays a role in enhancing effective management in PLHIV. Addressing ADRs at the earliest, with necessary treatment modifications and timely counseling would markedly improve adherence to treatment and ensure better quality of life among PLHIV.

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Conflicts of interest

There are no conflicts of interest.

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