Tenofovir Based First Line Therapy in Newly Diagnosed Case of HIV Infection: An Experience from a Tertiary Care Hospital in India

Arkapal Bandyopadhyay (drarkapal@gmail.com)
All India Institute of Medical Sciences - Raipur https://orcid.org/0000-0001-9755-0233
Sarika Palepu
Bhavna Saini
Rakesh Chandra Chaurasia
Rakesh Kumar Yadav

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Abstract

Introduction: India has a huge burden of HIV/AIDS infection. Tenofovir based first line therapy is the preferred treatment for newly diagnosed cases with HIV infection.

Methodology: The present prospective study was done among newly diagnosed cases of HIV infection. The patients were followed up for a period of 6 months from the day of enrolment. Sociodemographic parameters, CD4 counts and adverse drug reactions were analysed at baseline and after 6 months. Bi-variate and multi-variate logistic regression was performed with the outcome variable as occurrence of adverse drug reactions.

Result: In this study, 67 patients were enrolled with mean age 32.75 (± 14.39) years. Mean CD4 count at start of treatment was 241.5/mm3. Mean difference in CD4 count was 383.05/mm3 (SD = 274.9). Dizziness, tingling, numbness of extremities and muscle cramps were most common adverse effects. On multi-variate logistic regression, 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.

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 the continuous burden of the disease is a global concern. In India, the burden of HIV/AIDS is constant in recent times. As per India HIV Estimation 2017 report, 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 2001-03 through 0.34% in 2007, 0.28% in 2012 and 0.26% in 2015 to 0.22% in 2017. Highly Active Antiretroviral therapy (HAART) forms the cornerstone of treatment of HIV infection.

Tenofovir disoproxil fumarate (TDF) + Lamivudine (3TC) + Efavirenz (EFV) combination was the preferred first-line antiretroviral therapy (ART) regimen for adults and adolescents according to WHO.[1] It has been implemented in India by National AIDS Control Organisation (NACO). Tenofovir disoproxil is a nucleotide analog reverse-transcriptase inhibitor (NtRTI). Lamivudine, a nucleoside analog, is a potent reverse transcriptase inhibitor. Efavirenz is classified as a non-nucleoside reverse-transcriptase inhibitor. Once daily Tenofovir based first line regimen has better compliance and has improved adverse drug reaction profile as compared to Zidovudine or Stavudine based therapy.

As TLE is categorised as the first line therapy in PLHIV, we intended to assess the adverse drug reactions in patients started on this regimen. The objectives of the present study were to assess adverse drug

reactions in patients newly receiving TLE regimen in a tertiary care hospital at Allahabad, Uttar Pradesh and also to study the association between selected variables and occurrence of adverse drug reactions.

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 centre over three 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 in 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 Efavirenz (600 mg) (TLE) one tablet, once daily as a standard regimen approved by WHO and implemented by the National AIDS Control Organisation (NACO). The patients were observed for a period of six months from the date of enrolment and followed up on monthly basis. The drugs were dispensed free of cost from the ART Centre of the institute. CD4 count was done as per standard guidelines. The patients with concomitant comorbidities continued to take their treatment.

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

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 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 were noted. A detailed drug reaction history was noted. Grading of the ADRs was done according to standard guidelines of WHO. The WHO- ADR probability scale and Naranjo's algorithm were used for causality assessment of the ADRs. Severity of the ADR was assessed by Modified Hartwig and Siegel Scale. Preventability of ADR was assessed by Modified Shummock and Thornton Scale.

In this study, Adverse Drug Reaction is defined as any response to a drug which is noxious and unintended, and which occurs at doses normally used in man. Poor adherence was defined as the patient missing one pill in the preceding week.

Data was collected and analysed in STATA version 14.0. Normality test was carried out on all continuous variables and presented as either mean ± standard deviation. Bi-variate logistic regression was done to assess the occurrence of adverse drug reactions with selected variables using chi square test. Variables which were found to be significant (at $p < 0.25$) were considered for inclusion in multi-variate analysis. Multi-variate logistic regression was performed with the outcome variable as occurrence of ADR (coded as binary). Variables with $p < 0.05$ on multi-variate logistic regression were considered significant. The study was approved by 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. Majority of the patients were females (53.7%), illiterate (41.8%), married (73.1%) and were unemployed or students by occupation (44.7%). Mean monthly income of the patients was 2,321 rupees. It was seen that majority of the patients belonged to nuclear family (85%) with no history of migration (86.6%). (Table-1)

Sl No	Characteristic		Results N (%)
1	Age Mean age (± SD)		3 – 65 years 32.75 (± 14.39)
2	Gender	Males	31 (46.3)
		Females	36 (53.7)
3	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)
		Post-graduate	6 (9.0)
4	Marital status	Married	49 (73.1)
		Unmarried	6 (9.0)
		Divorced	1 (1.5)
		Widow/Widower	1 (1.5)
		Separated	10 (14.9)
5	Occupation	Professional/ Semi-Professional	4 (6)
		Clerk/Shopkeeper/Farmer	2 (3)
		Skilled	4 (6)
		Semi-skilled	7 (10.4)
		Unskilled	18 (26.9)
		Unemployed/Student	30 (44.7)
		Home-maker	2 (3)
6	Mean monthly income (in rupees)		2,321 (0-15,000)
7	Family type	Nuclear	57 (85)
		Extended	10 (15)
8	History of migration	Yes	9 (13.4)
		No	58 (86.6)

9	High risk behaviour	Yes	65 (97)
		No	2 (3)
10	Mean (± SD) delay in treatment start (in days)		143.2 (± 493.05) Range - 0 to 2900
11	Mean CD4 count		241.5 Range: 32 - 496/mm3

Table 1
Socio-demographic characteristics of patients on TLE regimen
High risk behaviour was seen in most of the patients (97%). History of other comorbidities was positive in only 2 patients (11%). The mean delay in start of treatment was very high corresponding to 143.2 days. The mean CD4 count of the patients was low at the start of 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. Mean difference in CD4 count was 383.05 (SD = 274.9).

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

Sl No	Number of ADRs	N (%)
1	0	29 (43.3)
2	1	7 (10.4)
3	2	6 (9)
4	3	5 (7.5)
5	4	3 (4.4)
6	5	6 (9)
7	6	1 (1.5)
8	7	4 (6)
9	8	1(1.5)
10	9	3 (4.4)
11	10	2 (3)

Table 2
Adverse drug reactions in patients on TLE regimen
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%).

Majority of ADRs were of central nervous system (46.1%) followed by musculo-skeletal (18.2%) and gastro-intestinal (17.6%). 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). Most common ADR of musculo-skeletal system was painful muscle cramps (n = 23) followed by weakness (n = 15). Most common ADR of gastro-intestinal system was anorexia (n = 11) followed by increased appetite (n = 9), flatulence (n = 7), diarrhoea (n = 4) and gastritis (n = 4). 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)

Sl No	System involved	N (%)
1	Central Nervous system	76 (46.1)
2	Musculo-skeletal system	30 (18.2)
3	Gastro-intestinal system	29 (17.6)
4	Skin	15 (9.1)
5	Laboratory abnormalities	9 (5.4)
6	Miscellaneous	5 (3.0)
7	Cardio-vascular system	1 (0.6)
Total		165 (100)

Table 3
System-wise ADRs among patients on TLE regimen
The causality assessment done by 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% patients, probably preventable in 76.4% patients and not preventable in 13.2% patients. It was seen that 22 patients (32.8%) were non adherent to treatment during the study course.

Bi-variate logistic regression was done to assess the occurrence of ADRs with selected variables. It was seen that occurrence of ADRs was more in males, illiterate patients and those who were currently not working. However, on multi-variate logistic regression, occurrence of ADRs was seen to be significantly higher only in illiterate patients. (Table- 4)

Sl. No	Variable		Unadjusted OR p-value (95% CI)	Adjusted OR p-value (95% CI)
1	Age		1.01 0.41 (0.97 - 1.06)	-
2	Gender	Male	1	1
		Female	0.25 0.00 (0.08 - 0.70)	0.49 0.26 (0.14 - 1.70)
3	Education	Illiterate	1	1
		Literate	0.19 0.00 (0.06 - 0.57)	0.23 0.01 (0.07 - 0.75)
4	Occupation	Not working	1	1
		Working	0.29 0.01 (0.10 -0.81)	0.44 0.18 (0.12 -1.49)
5	Family type	Nuclear	1	-
		Extended	1.17 0.82 (0.29 - 4.60)	
6	History of migration	Yes	1	-
		No	1.77 0.42 (0.43 - 7.28)	
7	Delay in treatment start	No	1	-
		Yes	1.56 0.37 (0.57 - 4.21)	
8	CD4 count	<250	1	-
		≥250	1.27 0.62 (0.48 - 3.38)	
9	Adherence	Good	1	-

Table 4
Association of ADRs with select socio-demographic variables

Discussion:

The present study evaluated the occurrence of adverse drug reactions to Tenofovir based first line ART regimen amongst patients attending tertiary care hospital in Allahabad.

In the present study, 53% were females. In a study by Chowta N M et al, it was observed that 53.8% were females amongst patients on Tenofovir regimen, similar to our study. In the present study, it was seen that there was a wide range of delay in 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 meagre income. These factors might have affected treatment seeking behaviour. 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 was 241.5 cells/mm^3 in our study. In a study by Neera Samar et al, CD4 counts of majority of the patients on TLE regimen ranged between 201–350 cells/mm^3 similar to our study. It was also seen that the mean difference in CD4 values deteriorated in 10 patients (range from − 8 to -407) and improved in 20 patients in the present study. Reasons behind the deterioration in CD4 count was not analysed in the study participants.

In the present study, no ADRs were observed in 42.1% of patients. Majority of the ADRs were amongst males and were in the age group of 15–45 years. In a study by Hemasri et al, no ADRs were seen in 42.18% patients on TLE regimen similar to our study. In the present study, majority of the ADRs belonged to central nervous, musculo-skeletal and gastro-intestinal system. In a study by Chauhan SN et al, 42% of the ADRs belonged to Central Nervous system similar to our study. In a study by Joseph et al, similar findings were seen as fatigue, headache, nausea and vomiting were most common ADRs. In a study by Neera Samar et al, [4] majority of the ADRs were of neuropsychiatric manifestations similar to our study.

The causality assessment by WHO-UMC scale showed that 58.0% of ADRs were Possible. However, in a study by Chauhan SN et al,[8] 83% of ADRs on TLE regimen were categorised 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 SN 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, analysing adverse drug reactions to ART regimens, first line regimens in particular forms a mainstay of treatment course. Multitude of factors play a role in enhancing effective management in PLHIV. Addressing ADRs at the earliest, with necessary treatment modifications and timely counselling would markedly improve adherence to treatment and ensure better quality of life among PLHIV.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

Ethics approval and consent to participate

Participants were enrolled in the study after obtaining a written informed consent

Consent for publication

Yes

Availability of data and materials

Yes

Competing interests

Nil

Funding

Nil

Authors' contributions

_	Author 1	Author 2	Author 3	Author 4	Author 5
Concepts	▯				
Design	▯	▯			
Definition of intellectual content	▯	▯			▯
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