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Efficacy and safety of 400 mg efavirenz versus standard 600 mg dose when taken with tenofovir and lamivudine combination in Indian adult patients with HIV-1 infection

An open-label, interventional, randomized, non-inferiority trial

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Abstract

Background: To evaluate the non-inferiority of low dose efavirenz (400 mg) to standard dose efavirenz (600 mg), when taken in combination with tenofovir and lamivudine in Indian patients with HIV-1 infection.

Methods: An open-label, interventional phase IV study with blinded assessment was conducted across 17 sites in India. HIV-1-infected antiretroviral therapy-naive adult patients (≥18 years of age) with a plasma HIV-1 viral load of at least 1000 copies per mL were randomized to receive either tenofovir/lamivudine/efavirenz (TLE) 400 or TLE 600. The primary endpoint was the difference in the proportion of patients achieving < 200 copies per mL at the end of 24 weeks.

Results: A total of 265 patients were enrolled and were randomized in 1:1 ratio to TLE 400 group (130 patients) and TLE 600 group (135 patients). At week 24, the proportion of patients with a viral load of less than 200 copies per mL was 80.70% for TLE 400 and 78.95% for TLE 600 (difference 1.75%, 90% confidence interval: –7.01, 10.49) which was within the predefined margin of –10% (90% confidence interval). Significantly lower study drug-related adverse events were observed in TLE 400 group compared to TLE 600 group (52.30%, n = 68 vs 64.92%, n = 87; *P* = .037). The treatment discontinuation percentage was marginally higher by 2.08% in TLE 600 group.

Conclusion: The fixed-dose combination of TLE 400 is non-inferior to TLE 600 in terms of viral suppression and has an improved safety profile over 24 weeks in adult Indian patients with HIV-1 infection.

Abbreviations: ART = antiretroviral therapy, CI = confidence interval, CNS = central nervous system, FAS = full analysis set, HIV = human immunodeficiency virus, NRTI = nucleoside reverse transcriptase inhibitor, RAS = randomised analysis set, TLE = tenofovir/lamivudine/efavirenz, WHO = World Health Organisation.

Keywords: efavirenz, HIV-1 infection, lamivudine, safety, tenofovir

All data have been approved for publication.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

More than 2 million people are living with human immunodeficiency virus (HIV) infection as of 2019 in India.[1] The prevalence of HIV infection is 0.22% in the age group 15 to 49 years and the incidence is 0.05 per 1000 uninfected population.[1] Currently HIV infection is being well-managed with highly active antiretroviral therapy that decelerates the disease progression and improves survival rate.[2] The results from clinical trials, TEMPRANO and START, have revealed that early commencement of antiretroviral therapy (ART) reduces the risk of adverse clinical conditions, the progression to acquired immunodeficiency syndrome, and mortality.[3,4] The standard prescribed ART comprises of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors, integrase strand transfer inhibitor and protease inhibitors.[5,6] Efavirenz is an non-nucleoside reverse transcriptase inhibitors which is commonly used in combination with NRTIs as a standard ART.[6]

The United States Food and Drug Administration approved efavirenz at a 600 mg dose through an accelerated review process in 1998[7] and the same was approved in 2008 in India.[8] The drug has been co-formulated with other antiretroviral drugs and found to be effective but with high incidence of neuropsychiatric adverse events and suicidal tendency.[9–12] In 2018, a lower dose of efavirenz (400 mg) was approved in combination with lamivudine and tenofovir in USA.[13] This approval of a lower dose is based on the outcomes of the global ENCORE1 trial. This multicentre trial concluded that a low dose of 400 mg efavirenz was non-inferior to the standard dose of 600 mg when administered along with tenofovir and emtricitabine over a duration of 48 weeks.[16] Further, 96-week follow-up of this trial reported fewer patients with AEs due to efavirenz 400 mg than 600 mg. Based on the positive outcomes of the ENCORE1 trial, the World Health Organisation (WHO) suggests the use of low dose efavirenz (400 mg) in combination with NRTI as an alternate first line regimen for adults and adolescents with HIV infection initiating ART.[14]

In India, low dose efavirenz in combination with tenofovir and lamivudine, [tenofovir/lamivudine/efavirenz (TLE 400)] was approved by Drugs Controller General of India in 2017.[15] However, there is a lack of efficacy and safety data of this fixed dose combination. Hence based on the suggestions of Drugs Controller General of India, this study was conducted to evaluate the efficacy and safety of TLE 400 combination in the Indian population. This paper reports the outcomes of the study that evaluated the non-inferiority of TLE 400 versus TLE 600 in Indian patients with HIV-1 infection.

2. Methods

2.1. Study design

This was a multicentre, open label, randomized prospective, interventional phase IV, non-inferiority study (CTRI/2017/11/010679) conducted with blinded assessment. The study was conducted across 17 sites in India, between January 2018 and October 2019, and included ART treatment naïve adult Indian patients with HIV-1 infection. The eligible participants were randomized (1:1) to receive either TLE 400 or TLE 600. The investigator as well as the patient were not blinded to treatment assignments. To minimize bias, the treatment assignments were not revealed to the central laboratory for efficacy (HIV-1 RNA) analysis and the study site team responsible for safety assessments. The randomization list was generated by an independent statistician. The treatment group codes/descriptions, along with the randomization list, were supplied in blinded manner to the designated personnel involved in dispensing and dosing of investigational products.

The total duration of the study was approximately 31 weeks; screening period of up to 3 weeks, treatment duration of 24 weeks and safety follow-up visits of 4 weeks. Telephonic follow-up was done at week 8 and week 18 to ensure treatment compliance. The study was approved by respective independent ethics committees (IEC) prior to study initiation (Details of IECs are provided in the Supplemental Digital Content, http://links.lww.com/MD/I3) and a signed written informed consent was obtained from each patient before enrollment in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonisation-Good Clinical Practice (ICH-GCP).

2.2. Study population

Adult patients (≥18 years of age) with a confirmed diagnosis of HIV-1 infection was the main eligibility criteria. The other inclusion criteria for this study included; patients of either sex, body mass index of ≥ 18 kg/m^2, plasma HIV-1 viral load of at least 1000 copies per mL, no previous (ART) and/or use of any investigational drug or device within 30 days or 5 half-lives of an investigational drug, whichever is longer. Females with the childbearing potential needed a negative pregnancy test at screening and the baseline and sexually active heterosexual patients were required to use 2 effective methods of contraception. Patients with previous acquired immunodeficiency syndrome defining illness, any uncontrolled opportunistic infection or malignancy, absolute neutrophil count and platelet count lower than 500 and 50,000 cells per μL respectively, hemoglobin ≤ 7 g/dL or 4.34 mmol/L, serum transaminases more than 5-times the upper limit of normal, clinically relevant drug or alcohol abuse within 12 months of screening, and renal impairment (estimated glomerular filtration rate < 50 mL/minute/1.73 m^2) were excluded from the study.

2.3. Study treatment and assessments

At screening, the demographic data including age, gender, predominant race, ethnicity, height, and weight, smoking status and risk category for HIV transmission and relevant medical history/medication was collected. Screening for HIV, genotyping and physical examination was done. Other screening procedures including electrocardiogram, plasma HIV-1 viral load, urine/blood tests for drug or alcohol abuse and estimated glomerular filtration rate assessment was performed.

All eligible patients in the study received one tablet of either TLE 400 or TLE 600 based on the randomization schedule, each treatment, once daily on an empty stomach, at bedtime. At week 4, 12, 24 and 28 (±3 days) visits, the patients underwent physical examination, vital signs evaluation and concomitant medications were recorded. For women of childbearing potential who have not been surgically sterilized, a serum pregnancy test was conducted at screening and at the safety follow-up visit and more frequently if clinically indicated.

2.4. Study endpoints

The primary endpoint was to assess the proportion of patients with plasma HIV-1 viral load of less than 200 copies per mL at week 24. The non-inferiority of the treatment group was established if the lower bound of 90% 2-sided confidence interval (CI) for the difference in viral load exceeded the margin of −10%. The secondary endpoint included the assessment of the safety and tolerability of TLE 400 versus TLE 600.

2.5. Sample size calculation

The sample size was computed to ensure sufficient statistical power to establish the non-inferiority of Efavirenz 400 mg

fixed dose combination to Efavirenz 600 mg fixed dose combination. Based on the published results and literature, an equal antiretroviral response rate of 90% and a non-inferiority margin of 10% were assumed for the sample size. By considering 80% statistical power and a type-I error rate of 0.05 (one sided), the sample size was estimated to be 112 patients per arm (a total of 224 evaluable patients) in the Per protocol set to establish the non-inferiority of lower limit of 95% (one sided) CI for the difference in antiretroviral response rate between Efavirenz 400 mg and Efavirenz 600 mg to exceed the non-inferiority margin of –10%. The sample size was adjusted to be 125 randomized patients per arm or 250 randomized patients in total by allowing 10% major protocol deviations in the study.

2.6. Statistical methods

The statistical analysis was performed using Statistical Analysis System (SAS® version 9.4). The primary objective was tested by constructing 2-sided 90% CI and one sided 95% CI using Newcombe-Wilson score method for the proportional difference between the 2 treatment groups. Descriptive statistics included summary statistics (number of observations, mean, standard deviation, minimum, median, and maximum) for continuous data and frequency counts and percentages for categorical data.

Full analysis set (FAS) included all treatment allocated patients with at least one post-baseline evaluable efficacy assessment. Safety analysis set included all the patients who received at least one dose of study drug. Randomised analysis set (RAS) included all patients who were randomized for the treatment and all patients with non-missing randomization number. Per protocol set included all the patients who received study treatment, had evaluable HIV-1 RNA levels at week 24 and had no major protocol deviations.

3. Results

3.1. Patient disposition

A total of 348 patients were screened, of which 265 patients were enrolled in the study, and then randomized in 1:1 ratio to TLE 400 group (130 patients) and TLE 600 group (135 patients). Figure 1 shows the disposition of patients in this clinical study.

3.2. Patient demographics

The patient demographics at baseline are summarized in Table 1. The proportion of males and females, mean age, and mean height of patients were similar in both the groups. The weight and body mass index of the patients in TLE 600 group was higher than TLE 400 group and were statistically significant. The mean CD4 cell count was 329.37 and 306.87 at baseline, in TLE 400 and TLE 600 group respectively. The mean HIV-1 RNA viral load count (log 10 transformed) was 4.74 in TLE 400 group and 4.76 in TLE 600 group.

3.3. Efficacy analysis

The primary efficacy analysis was performed on the Per protocol set in which the proportion of patients with plasma HIV-1 RNA viral load of less than 200 copies per mL was 80.70%

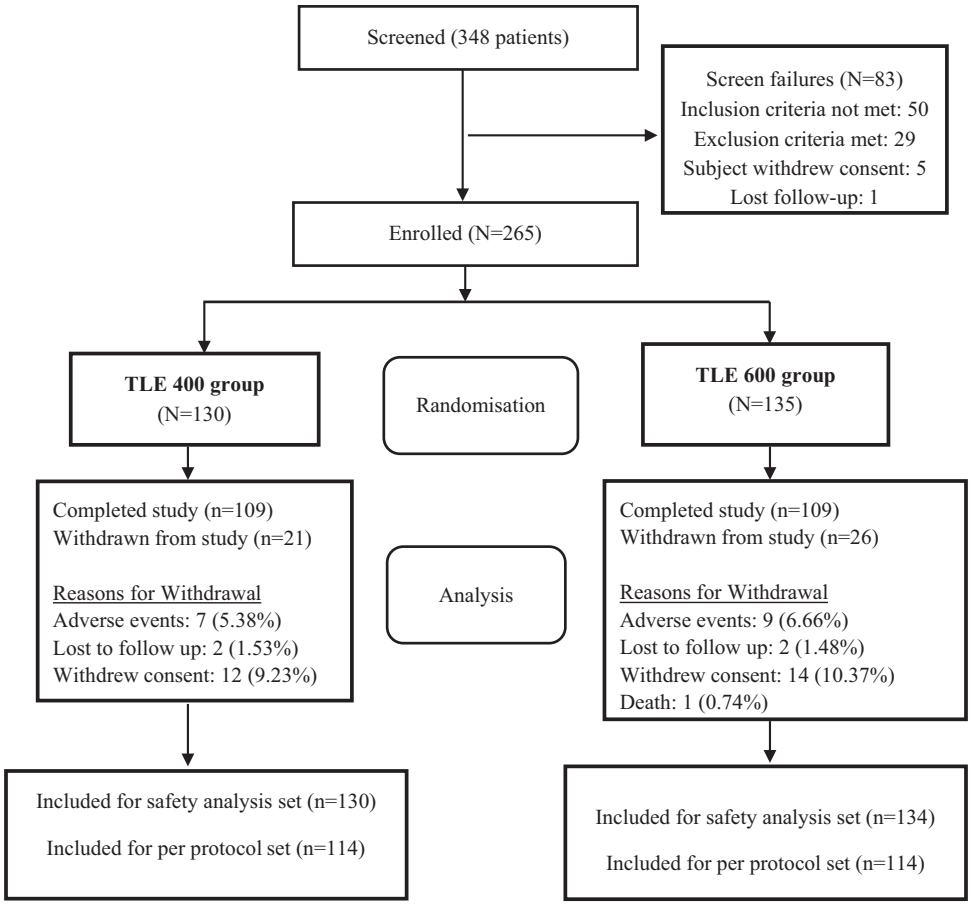

Figure 1. Patient disposition. n = total number of patients in a given category and treatment group, N = total number of patients in the specified treatment group, TLE = tenofovir/lamivudine/efavirenz.

Table 1

Patient demographics

Variable	TLE 400 (N = 130)	TLE 600 (N = 135)	*P* value
Gender n (%)			
Male	72 (55.38)	75 (55.55)	.978
Female	58 (44.62)	60 (44.45)	
Age, years	38.35 (10.14)	39.28 (9.31)	.438
Height	158.26 (9.69)	158. 77 (9.23)	.6623
Weight	56.33 (10.89)	59.34 (12.94)	.041
BMI, kg/m^2	22.37 (3.16)	23.45 (4.27)	.020
Childbearing potential	37 (28.46)	43 (31.85)	.360
CD4 cell count	n = 126	n = 134	.400
	329.37 (231.44)	306.87 (198.95)	
HIV–1 RNA viral load Count	288418.30 (740112.79)	239218.00 (411115.97)	.506
HIV–1 RNA viral load Count (Log 10 transformed)	4.74 (0.93)	4.76 (0.93)	.884

Data is presented as mean (SD) unless otherwise specified.

BMI = body mass index, CD4 = cluster of differentiation, HIV = human immunodeficiency virus, n = total number of patients in a given category and treatment group, N = total number of patients in the specified treatment group, RNA = ribonucleic acid, TLE = tenofovir/lamivudine/efavirenz.

(n = 92) in TLE 400 group and 78.95% (n = 90) in TLE 600 group at the end of 24 weeks. The difference in proportion was 1.75% with a 90% CI: –7.01, 10.49. The lower bound of 90% confidence limit (–7.01%) was above the predefined non-inferiority margin of –10%. The 95% CI for difference in proportion was (–8.69, 12.16). Sensitivity analyses was conducted using FAS and RAS and the difference in proportion was 2.07% (90% CI: –6.68, 10.75) and 2.62% (90% CI: –6.67, 11.82) for FAS and RAS respectively. The 95% CI for the difference in proportion for FAS was (–8.36, 12.41) and for RAS was (–8.43, 13.54). The lower bound of both 90% and 95% CI for the difference in proportion was above the predefined non-inferiority margin of –10% in all sensitivity analyses (Table 2).

At baseline for FAS, the mean of actual CD4 cell counts of TLE 400 and TLE 600 group were 324.00 and 318.30 respectively, which was comparable between the 2 groups. At week 24, the mean of actual CD4 cell counts were 472.00 and 424.60 and the mean change in CD4 cell counts from baseline was 155.10 and 107.30 in TLE 400 group and TLE 600 group respectively.

For FAS at baseline, the mean of log transformed plasma HIV viral load of TLE 400 group and TLE 600 group were 4.70 and 4.80 respectively, while the values at week 24 were 1.60 and 1.70 respectively. The mean, plasma HIV viral load (log 10 transformed) showed a decrease in the value from baseline to week 24. The changes from baseline to week 24 was comparable between TLE 400 (–3.20) and TLE 600 groups (–3.10) with a difference of –0.07 (95%C I: –0.454, 0.327) (Table 3).

3.4. Safety analysis

The safety analysis set comprised of 130 patients in TLE 400 group and 134 patients in TLE 600 group. Of these, 84 (64.61%) patients in TLE 400 group had 381 AEs and 110 (82.08%) patients in TLE 600 group had 554 AEs. Adverse events related to the study treatment were seen in 68 patients (52.30%); in TLE 400 group and 87 patients (64.92%) in TLE 600 group. Seven (5.38%) patients in TLE 400 group and 10 (7.46%) patients in TLE 600 group discontinued the study medication. Two patients died during the study in TLE 600 group, and no deaths were reported in TLE400 group.

Majority of the AEs reported were mild in severity in both the groups. No serious AEs (SAEs) were reported in the TLE 400 group, while 3 patients (2.23%) reported SAEs in TLE 600 group, of which 2 patients (1.49%) had fatal outcome. None of the SAEs were related to the study treatment (Table 4).

Table 5 summarizes the number of patients with AEs (≥5%) classified by preferred term. Based on the System Organ class, the most frequently reported AEs (≥5%) in both TLE 400 and TLE 600 groups included nervous system disorders [98 events in 41 patients; 31.53% vs 148 events in 61 patients; 45.52%, respectively ($P = .020$)], gastrointestinal disorders [56 events in 30 patients; 23.07% vs 98 events in 48 patients 35.82%, respectively ($P = .023$)]; and psychiatric disorders [56 events in 18 patients; 13.84% vs 50 events in 31 patients; 23.13%, respectively ($P = .052$)].

Table 6 shows the percentage of patients reporting AEs as categorized by efavirenz product information. The incidence of central nervous system (CNS) related AEs were maximum (31.53%, n = 41 in TLE 400 group vs 44.77%, n = 60 in TLE

Table 2

Analysis of patients with plasma HIV-1 RNA viral load of < 200 copies/mL at week 24

		TLE 400	TLE 600			
Analysis	Analysis set	n (%)	n (%)	Diff. in proportion	90% CI*	95% CI*
Primary analysis	PPS	92 (80.70)	90 (78.95)	1.75	(–7.01, 10.49)	(–8.69, 12.16)
Sensitivity analysis	FAS	92 (80.70)	92 (78.63)	2.07	(–6.68, 10.75)	(–8.36, 12.41)
	RAS	92 (70.77)	92 (68.15)	2.62	(–6.67, 11.82)	(–8.43, 13.54)

Patients with missing Week 24 HIV-RNA results are considered as non-responder.

Percentages are based on the total number of patients in the specified treatment group under per protocol set.

* Two-sided 90% CI and 95% CI was constructed using Newcombe-Wilson score method for computing CI for proportion difference.

CI = confidence interval, FAS = full analysis set, HIV = human immunodeficiency virus, n = total number of patients with plasma HIV-RNA viral load less than 200 copies/mL, PPS = per protocol set, RAS = randomised analysis set, RNA = ribonucleic acid, TLE = tenofovir/lamivudine/efavirenz.

Table 3

Analysis of actual and change from baseline in CD4 cell count and plasma HIV viral load by visit–log 10 transformed value. (Full analysis set)

Parameter		TLE 400 (N = 114)		TLE 600 (N = 117)		*P* value
		Actual	Change from baseline	Actual	Change from baseline	
CD4 cell count						
Baseline	N	110	–	117	–	–
	Mean (SD)	324 (223.80)		318.3 (204.80)		
Week 24	N	111	107	114	114	.057
	Mean (SD)	472.0 (232.50)	155.10 (184.40)	424.6 (254.70)	107.30 (186.90)	
Plasma HIV viral load by visit–log 10 transformed value						
Baseline	N	114	–	114		–
	Mean (SD)	4.70 (0.90)		4.80 (0.90)		
Week 24	N	114	–3.20 (1.40)	114	–3.10 ± 1.50	.742
	Mean (SD)	1.60 (1.20)		1.70 (1.40)		
Difference (95% CI)		–0.07 (–0.454, 0.324)				

CD4 = cluster of differentiation 4, CI = confidence interval, HIV = human immunodeficiency virus, N = total number of patients in the specified treatment group, SD = standard deviation, TLE = tenofovir/lamivudine/efavirenz.

Table 4

Overall summary of adverse events (Safety analysis set)

Parameter	TLE 400 (N = 130)		TLE 600 (N = 134)		*P* value
	Number of events	n (%)	Number of events	n (%)	
Adverse events	381	84 (64.61)	554	110 (82.08)	.001#
Serious adverse events	–	–	3	3 (2.23)	.247*
Adverse event related to study drug	261	68 (52.30)	379	87 (64.92)	.037#
Adverse events leading to study medication discontinuation	8	7 (5.38)	11	10 (7.46)	.492#
Adverse events leading to death	0	–	2	2 (1.49)	.498*
Adverse events by maximum severity					
Mild	241	60 (46.15)	368	74 (55.22)	
Moderate	38	21 (16.15)	64	30 (22.38)	
Severe	5	3 (2.30)	8	6 (4.47)	.011*

**P* value calculated by Fisher exact test;

#*P* value calculated by Chi-Square test.

n = number of patients in a given category and treatment group, N = total number of patients in the specified treatment group, TLE = tenofovir/lamivudine/efavirenz.

600 group, $P = .027$) and respiratory system associated AEs were the least (8.46%, n = 11 in TLE 400 vs 8.95%, n = 12 in TLE 600 group, $P = .887$) in both groups.

4. Discussion

In this study, the non-inferiority of the low dose efavirenz in combination with lamivudine and tenofovir compared to the standard dose of efavirenz with the same combination in the Indian population was established. The current study and the ENCORE1 trial are similar in terms of comparing the non-inferiority of low dose efavirenz, but the NRTI combination used is different. However, this difference will have minimal impact, as emtricitabine and lamivudine are clinically equivalent.[16] The findings from this study are consistent with findings of previously published investigations on efavirenz comprising regimen.[17–20]

The results obtained during the 24 weeks of treatment in ART-naive adult Indian patients with HIV-1 infection, showed 80.70% of patients achieving reduction of HIV viral load of less than 200 copies per mL in the TLE 400 group compared to 78.95% of patients in the TLE 600 group. A similar trend was seen in ENCORE1 trial with viral suppression of 94.10% for low dose efavirenz and 92.20% for standard dose efavirenz in combination with tenofovir and emtricitabine (difference 1.85%, 95% CI: –2.10, 5.79). At week 24, the CD4 cell count was found to be higher in patients who received 400 mg of efavirenz as compared to those who received 600 mg; however, this difference was not statistically significant. This was an appreciable trend and is in line with the results from the ENCORE1 trial. A recent study conducted in Pune, India to explore the combination of TLE 400 single dose regimen as a first line switch strategy found that TLE 400 exhibits good efficacy and safety specially for patients who are virologically suppressed on TLE 600.[21] The current study further supports the effectiveness of TLE 400 compared to TLE 600.

This study reported less CNS related AEs with the lower dose of efavirenz which is a clinically relevant outcome. The ENCORE1 trial reported significantly more frequent AEs in 600 mg efavirenz group than in the 400 mg efavirenz group (difference –10.50%, 95% CI: –18.20, –2.80; $P = .01$).

In the present study, the treatment discontinuation was found to be higher by 2.08% in the TLE 600 group, thus it can be inferred that a lower dose of efavirenz was associated with fewer AEs and fewer treatment discontinuations. There were no SAEs and deaths in the TLE 400 group whereas the TLE 600 group reported 3 SAEs and 2 deaths. In ENCORE1 trial, study drug-related AEs were significantly more frequent in the 600 mg group than in the 400 mg group (47%, n = 146 vs 37%, n = 118; difference –10.50%, 95% CI: –18.20, –2.80; $P = .01$) and significantly fewer patients in 400 mg group discontinued the treatment (400 mg: 2%, n = 6 vs 600 mg: 6%, n = 18; difference –3.96%, 95% CI: –6.96, –0.95; $P = .01$). These findings were in accordance with the previously reported non-inferiority clinical trials.[17,21–23]

Table 5

Number of patients with adverse events classified by preferred term (with ≥ 5% AEs)

	TLE 400 (N = 130)		TLE 600 (N = 134)		
System organ class preferred term	**Number of events**	**n (%)**	**Number of events**	**n (%)**	***P* value**
Number of patients with at least one adverse event	381	84 (64.61)	554	110 (82.08)	.001
Ear and labyrinth disorders	11	11 (8.46)	20	18 (13.43)	.197
Vertigo	10	10 (7.69)	19	17 (12.68)	.181
Gastrointestinal disorders	56	30 (23.07)	98	48 (35.82)	.023
Abdominal pain	2	2 (1.53)	11	9 (6.71)	.035
Diarrhoea	7	7 (5.38)	22	15 (11.19)	.088
Nausea	13	7 (5.38)	12	10 (7.46)	.492
Vomiting	13	12 (9.23)	27	17 (12.68)	.369
General disorders and administration site conditions	47	26 (20.00)	64	41 (30.59)	.048
Asthenia	18	15 (11.53)	32	24 (17.91)	.145
Pyrexia	10	8 (6.15)	20	17 (12.68)	.070
Infections and infestations	20	16 (12.30)	29	23 (17.16)	.266
Urinary tract infection	10	8 (6.15)	13	11 (8.20)	.518
Investigations	12	11 (8.46)	25	19 (14.17)	.143
Hepatic enzyme increased	1	1 (0.76)	9	8 (5.97)	.036
Metabolism and nutrition disorders	19	15 (11.53)	25	19 (14.17)	.522
Dyslipidaemia	11	10 (7.69)	19	16 (11.94)	.247
Nervous system disorders	98	41 (31.53)	148	61 (45.52)	.020
Dizziness	35	31 (23.84)	63	37 (27.61)	.484
Head discomfort	8	6 (4.61)	11	8 (5.97)	.623
Headache	39	16 (12.30)	40	31 (23.13)	.022
Somnolence	9	8 (6.15)	17	15 (11.19)	.147
Psychiatric disorders	56	18 (13.84)	50	31 (23.13)	.052
Insomnia	10	6 (4.61)	10	9 (6.71)	.461
Skin and subcutaneous tissue disorders	24	16 (12.30)	33	26 (19.40)	.115
Rash	12	12 (9.23)	18	17 (12.68)	.369

n = number of patients in a given category and treatment group, N = total number of patients in the specified treatment group, TLE = tenofovir/lamivudine/efavirenz.

Table 6

Adverse events as categorized by efavirenz product information

	TLE 400 (N = 130) n (%)	TLE 600 (N = 134) n (%)	*P* value
Central Nervous System	41 (31.53)	60 (44.77)	.027
Rash	13 (10.00)	19 (14.17)	.298
Gastrointestinal System	27 (20.76)	38 (28.35)	.152
Respiratory system	11 (8.46)	12 (8.95)	.887
Psychiatric	13 (10.00)	18 (13.43)	.386

n = number of patients in a given category and treatment group, N = total number of patients in the specified treatment group, TLE = tenofovir/lamivudine/efavirenz.

The limitation of the study is it's an open label study with both the investigator and the patient being aware of the treatment received. However, this was overcome by using laboratory parameter as the primary efficacy endpoint and the clinical laboratory was blinded to the treatment assigned.

In a recent update from WHO in 2019, for the first line antiretroviral regimens, efavirenz at low dose (400 mg) in combination with an NRTI backbone has been recommended as the alternative first line regimen for adults and adolescents with HIV and initiating ART. This study demonstrates comparable viral suppression of efavirenz 400 mg with 600 mg which further validates the updated WHO recommendation.[14,24] Thus, low dose efavirenz could be endorsed to be used as a part of routine HIV-1 management.

Dolutegravir in combination with NRTIs is the preferred first line regimen.[14] The New Antiretroviral and Monitoring Strategies in HIV-Infected Adults in Low-Income Countries (NAMSAL) trial conducted in Cameroon established the non-inferiority of lower dose efavirenz compared to dolutegravir-based regimen with regard to viral suppression.[24] This highlights the effectiveness of lower dose efavirenz which is in line with the outcomes of the current study. Further cost-effectiveness of the lower dose of efavirenz is warranted by a decrease in the manufacturing cost of the lower dose, improved safety profile and availability of the generic for the fixed dose combination of TLE 400. A lower dose will bring a corresponding decrease in the active pharmaceutical ingredient by 33% thereby reducing the product cost.[25] Thus, the lower dose of efavirenz will have a significant impact on the cost to treatment for patients with HIV-1 infection.

In summary, the results of this study indicate that a lower dose of efavirenz (400 mg) is non-inferior to the standard dose of 600 mg in terms of viral suppression, when combined with tenofovir and lamivudine during 24 weeks in ART-naive adult Indian patients with HIV-1 infection. This study also highlights an improved safety profile and reduced CNS related AEs in patients who received a lower dose combination of efavirenz.

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All the authors were involved in patient care and monitoring, study conceptualization, data collection, data analysis, results interpretation, and supervised manuscript writing. All authors had access to the study data and reviewed and approved the final manuscript.

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