

A Phase IV Study on Safety, Tolerability and Efficacy of Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate in Treatment Naïve Adult Indian Patients Living with HIV-1

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Purpose: WHO recommends dolutegravir (DTG) based regimens as first-line treatment for HIV-1 infection. However, few studies have been conducted in Indian population. Hence, our study evaluated the safety, tolerability, and efficacy of DTG 50 mg with Tenofovir and Lamivudine (300/300mg) fixed dose combination in treatment naïve adult Indian patients.

Methods: This was an open label, multicenter, prospective, interventional, phase IV study conducted across 14 sites between February 2019 and July 2020. 24 weeks was the treatment duration for each subject. The primary end point was to assess the incidence of adverse events (AEs) and secondary end points were to assess the proportion of patients achieving plasma HIV-1 RNA levels <50 copies/mL at week 24 and change in CD4+ cell count from the baseline. Safety analysis was conducted using Safety Analysis Set and efficacy analysis was carried out using Full Analysis Set and Per protocol set.

Results: A total of 288 patients were screened; 250 were enrolled; and 229 completed the study. 389 AEs were reported from 58% of patients. Of these, 61 were related to study treatment. One event of decreased creatinine clearance led to study discontinuation. One serious event of pyrexia was reported, which was unrelated to the study drug. The most common AEs were headache (18%), pyrexia (14%), vomiting (6.4%) and upper respiratory tract infections (6%). No deaths were reported. At week 24, 86.8% of the patients achieved plasma HIV-1 RNA levels <50 copies/mL and the mean CD4 cell count increased from 350.2 (SD, 239.73) at baseline to 494.6 (SD, 261.40) with an average increase of 143.2 (SD, 226.14) cells.

Conclusion: This study demonstrated the safety and efficacy of DTG based regimen in treatment naïve HIV-1 patients in Indian population and support use of DTG as first-line treatment regimen.

Keywords: HIV-1, dolutegravir, safety, efficacy, CD4 cell count, viral load, adverse events

Introduction

Human Immunodeficiency Virus Type 1 (HIV-1) remains a global health problem with an estimated 37.6 million people globally living with HIV-1 in 2020.¹ Most of these cases were reported from low and middle-

income countries (LMIC). In India, about 2.3 million people were living with HIV, with 0.22% prevalence in 2020.²

World Health Organization (WHO) 2016 guidelines recommend non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) based regimens as first-line antiretroviral therapy (ART).³ However, in many LMIC, there was increasing evidence of pretreatment HIV drug resistance (PDR) to NNRTIs.⁴ This led to low rates of virological suppression, acquisition of new mutations and high rates of ART discontinuation, especially with EFV.^{5–8} In response to this, WHO issued new guidelines recommending countries to move away from NNRTI regimens to dolutegravir (DTG) based regimens, in the regions with resistance $\geq 10\%$.^{9,10}

DTG is a potent second generation integrase strand transferase inhibitor (INSTI), with high rates of viral suppression, low rates of treatment discontinuation and high genetic barrier to develop HIV drug resistance in treatment naïve patients living with HIV-1.^{11–14} Furthermore, the drug shows rare severe side effects and has low rates of drug-drug interactions.¹⁵

In 2017, the generic DTG was introduced in India. All major guidelines^{16–19} and network meta-analysis (NMA)^{20–22} recommend DTG based regimens as preferred first-line ART in treatment naïve HIV patients. Also, DTG based regimens are now the standard of care in HIV treatment as per WHO guidelines.¹⁶ The National AIDS control organization recommend DTG 50 mg, in combination with Tenofovir (300mg) and Lamivudine (300mg) as preferred first line regimen for all PLHIV (age >10 years and weight >30kg).²³ However, there was limited data on exposure of Indian patients to DTG based regimens. So, the Indian regulatory agency, DCGI approved the product in India conditionally based on the global trials. However, the marketing authorization holder (Mylan) was required to conduct a phase IV study in India to characterize the safety and efficacy of DTG based regimens in Indian population. Hence, the study was designed as single arm, pragmatic clinical trial, designed to see if the DTG regimen is safe and efficacious when used as per the label. Therefore, the results of this study has maximum applicability and generalizability to evaluate if DTG regimen is working in the same way that is reported in preregistration clinical trials conducted by the originator.

The current study was planned to evaluate the safety, tolerability, and efficacy of once-daily DTG when given along with Tenofovir (TDF) and Lamivudine (3TC), in treatment naïve patients living with HIV-1.

Materials and Methods

Study Design

This was a Phase IV, Open-label, Multicenter, Prospective, Interventional Study, conducted in 250 HIV-1 positive patients in 14 sites across India from Feb 2019 to July 2020. The total duration of the study was approximately 28 weeks with a screening period of up to 3 weeks, study treatment period of 24 weeks and a safety follow-up period of 1 week (week 25) (Figure 1).

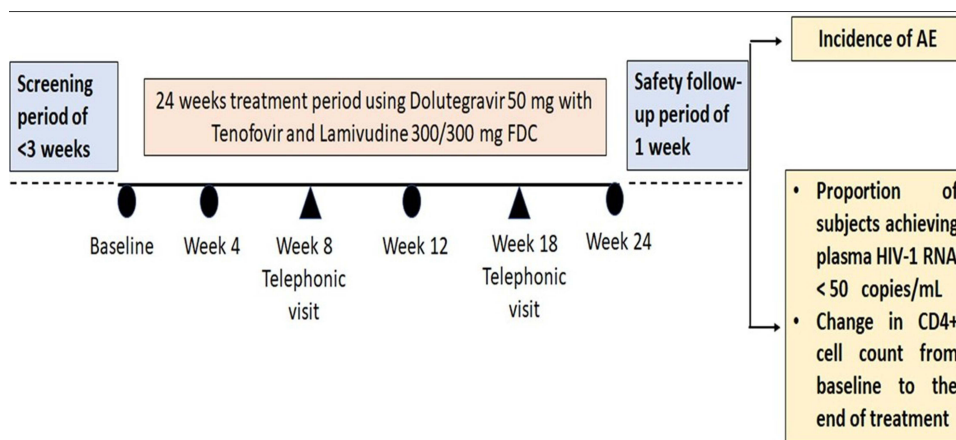


Figure 1 Overall schema of study design.

The study was carried out in accordance with the Declaration of Helsinki, ICH GCP guidelines (2016), New Drugs and Clinical trial Rules (2019) and National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017).

Study Population

Participants meeting the following inclusion criteria were enrolled in the study: Age ≥ 18 years, weight >40 kg, confirmed and documented HIV-1 infection, patients receiving ART therapy for the first time (treatment naïve).

Exclusion criteria include the following: Pregnant or nursing women, evidence of uncontrolled opportunistic infections or malignancy, absolute neutrophil count less than 500 cells per μL , estimated glomerular filtration (eGFR) rates <50 mL/min/1.73 m^2 , known hypersensitivity to any of the study drug. A full list of inclusion and exclusion criteria is provided in the [Supplementary File 1](#).

Study Procedures

Following the provision of informed consent, all the eligible patients at baseline (Day 1) received one tablet each of DTG (50 mg) and TDF and 3TC (300/300 mg) fixed dose combination once daily for 24 weeks.

The efficacy assessment was performed at week 24. Safety monitoring was performed throughout the study and included telephonic follow-up done at week 8, week 18 and week 25 to assess treatment compliance and for recording any adverse events (AEs). A subject diary was provided at baseline visit, and the physician reviewed it for drug compliance, at every site visit (week 4, 12 and 24).

Blood and urine samples were collected from the eligible patients at screening, week 12 and week 24 (end of treatment) for assessing renal and liver function tests, complete blood count, lipid profile and urine analysis. HIV-1 viral load and CD4 counts were performed at screening and week 24, serum pregnancy test at screening and week 24 (for women of childbearing potential), physical examination, weight and vitals were monitored at screening and all study visits.

Study Assessments and Endpoint

Safety was assessed by monitoring AEs, vital signs, 12-lead ECGs, physical examinations, and clinical laboratory test results. Any abnormality in these assessments from the baseline values were recorded as AEs or serious AEs (SAEs). Measuring the incidence of AEs during the study was the primary end point.

Efficacy was assessed using HIV-1 viral load and CD4 cell count. The proportion of patients achieving plasma HIV-1 RNA < 50 copies/mL at the end of treatment and change in CD4+ cell count from baseline to the end of treatment were the secondary endpoints assessed. Full details of the assessment are provided in [Supplementary File 2](#).

Statistical Analysis

A sample size of 250 was chosen for this study based on the primary endpoint of incidence of AEs reported. When the sample size is 250, the 95% two-sided confidence interval (CI) will provide a precision of at least 6.2% for the occurrence of any AE of interest, where the precision of estimation is defined as half width of 95% CI. Additionally, a sample size of 242 per arm was also used in the FDA registration study to evaluate the efficacy of dolutegravir in treatment naïve patients living with HIV-1.²⁶

Statistical processing was performed using Statistical Analysis System (SAS[®]). Descriptive statistics consist of summary statistics (number of observations, mean, standard error (SE), standard deviation (SD), minimum, median, and maximum) for continuous data and frequency counts and percentages for categorical data. The safety analyses were conducted using the Safety Analysis Set (SAF) which included all subjects who received at least one dose of the study treatment. AEs were tabulated according to the current version (version 22.1 or later) of the Medical Dictionary for Regulatory Activities (MedDRA) using Preferred Term (PT) within MedDRA System Organ Class (SOC). Frequencies and percentages were used to summarize treatment-emergent AEs (TEAEs), treatment-related AEs, AEs leading to discontinuation, and SAEs. Efficacy analysis was performed on Full Analysis Set (FAS) and repeated based on Per Protocol Set (PPS; all patients who received study treatment, had achieved both the end points, and had no major protocol deviations) as a supportive analysis. In FAS, patients with missing plasma HIV-1 RNA viral load were

considered as non-responders. Hence, FAS with complete cases was performed excluding the patients with missing data. The proportion of subjects achieving plasma HIV-1 viral load less than 50 copies per mL with Clopper–Pearson 95% CI were presented at the end of the study treatment visit. In addition, \log_{10} transformed value of change from baseline plasma HIV-1 viral load has been summarized descriptively. For CD4 cell counts, actual and change from screening cell counts have been summarized descriptively by visits. The 95% CI was constructed by using *t*-test statistics for the treatment group.

Results

A total of 288 patients were screened, of which 250 treatment naïve patients living with HIV-1 were enrolled; 38 patients did not meet inclusion/exclusion criteria. Of the 250 enrolled patients, 229 (91.6%) completed the study. Twenty-one (8.4%) patients failed to complete the study due to consent withdrawal [12 (4.8%) patients], lost to follow up [8 (3.2%) patients] and SAE/AE [1 (0.4%) patient]. Approximately 90% of the patients reported 80–125% compliance to the study treatment.

SAF included all enrolled 250 (100.0%) patients, whereas FAS included 227 (90.8%) patients as 23 (9.2%) patients did not have both HIV-1 RNA load, and CD4 cell counts at post-baseline visits, hence these patients were excluded from FAS. PPS included 211 (84.4%) patients, as 29 (11.6%) patients had missing HIV-1 RNA load and CD4 cell count, while 7 (2.8%) and 3 (1.2%) patients reported major protocol deviation and treatment non-compliance respectively and hence excluded from PP set (Figure 2).

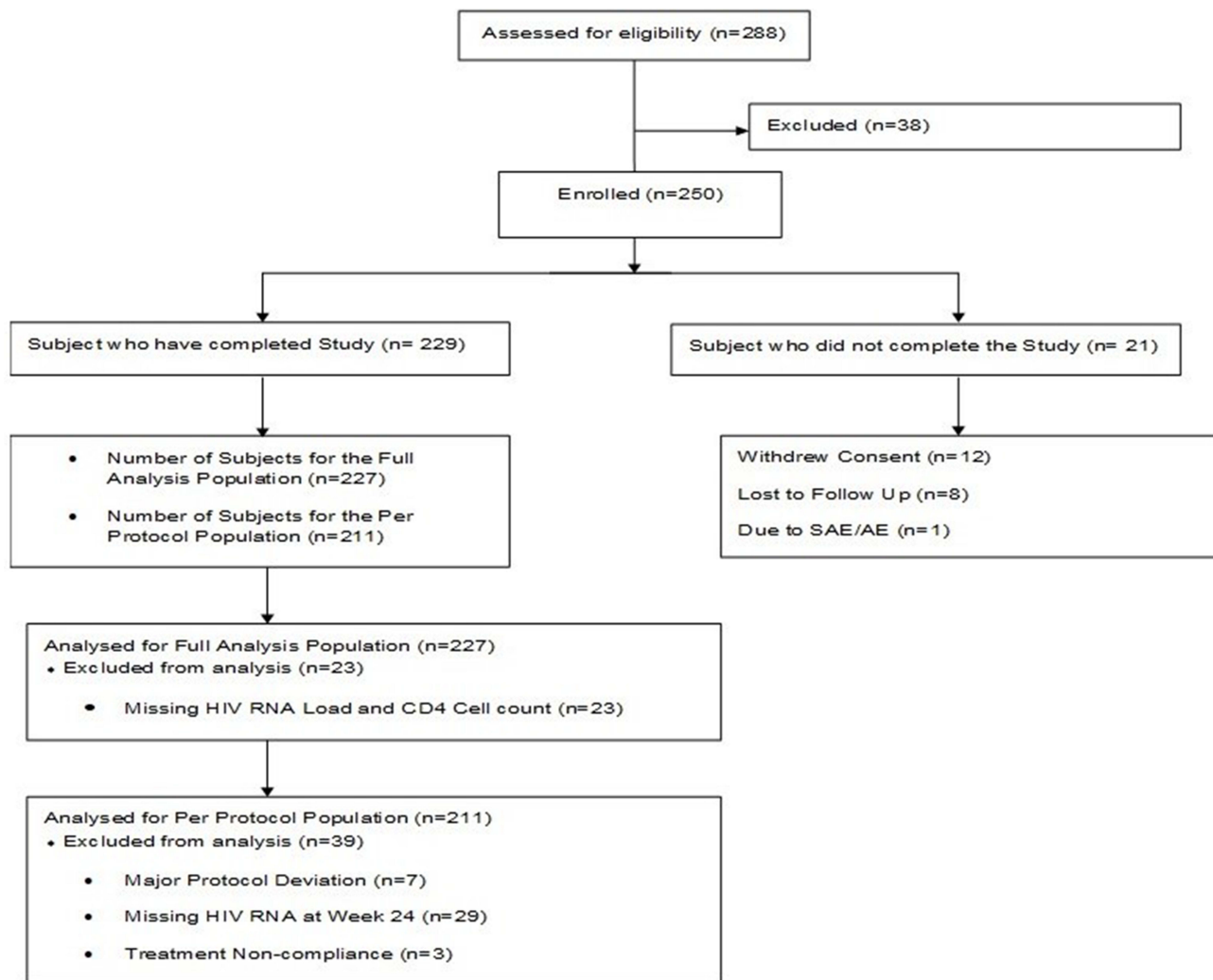


Figure 2 Disposition of subjects.

Demographic Characteristics

Of 250 enrolled patients, 145 (58.0%) were male, while 105 (42.0%) were female. The study cohort was Asian. The median (inter quartile range [IQR]) age and BMI of the cohort were 38.5 (18–70) years, and 22.2 (14.43–36.74) kg/m² respectively. The median (IQR) HIV-1 viral load (HIV RNA copies/mL) was 24,621.2 (10–5,500,145), and the mean CD4 cell counts (cells per cubic millimeter) (N = 249) was 350.3 ± 237.84 (Table 1).

Safety Evaluation

A total of 389 TEAEs were reported by 144 (57.6%) patients. Of these, 61 TEAEs reported from 36 (14.4%) patients were related to the study treatment; one event “decreased creatinine renal clearance” led to study medication discontinuation and early termination; one event of “Pyrexia” in 1 (0.4%) patient was a TESAE, which was not related to the study drug and patient recovered and completed the study. Further based on severity, of the total 250 enrolled patients, 110 (44.0%) patients had mild AEs, 33 (13.2%) patients had moderate AEs and 1 (0.4%, anemia) patient had a severe AE (Table 2).

Table 1 Summary of Demographics (All Enrolled Patients)

Parameters/Statistics N=250	Dolutegravir 50 mg (N=250) n (%)
Age (years)	
Median ± IQR	38.5 ± 18–70
Gender	
Male	145 (58.0%)
Female	105 (42.0%)
Race	
Asian	250 (100.0%)
BMI (kg/m ²)	
Median ± IQR	23.0 ± (14.43–36.74)
HIV-1 viral load (HIV RNA copies/mL)	
Median ± IQR	24621.2 ± (10–5,500,145)
CD4 cell counts (cells per cubic millimeter)	
N*	249
Mean ± SD	350.3 ± 237.84

Notes: *One Subject had CD4 results value as below 10 at screening, hence this subject was not included in Summary Statistics.

Abbreviations: N, total number; SD, standard deviation; BMI, body mass index; HIV-1, human immunodeficiency virus 1; RNA, Ribonucleic acid.

Table 2 Summary of Overall Treatment Emergent Adverse Events - Safety Set

Category	Dolutegravir 50 mg (N=250)	
	Number of Events	Subjects n (%)
TEAEs	389	144 (57.6%)
TESAE	1	1 (0.4%)
TEAEs related to study drug	61	36 (14.4%)
TEAEs Leading to Study Medication Discontinuation	1	1 (0.4%)
TEAE by maximum severity		
Mild	340	110 (44.0%)
Moderate	48	33 (13.2%)
Severe	1	1 (0.4%)

Abbreviations: TEAE, treatment emergent adverse events; TESAE, treatment emergent serious adverse events.

The most frequent AE reported was “headache” by 45 (18%) patients, followed by 40 events of “pyrexia” reported by 35 (14%) patients. Twenty-three events of “vomiting” were reported by 16 (6.4%) patients, 22 events of “upper respiratory tract infection” were reported by 15 (6%) patients. Additionally, 10 events of “rash” were reported by 8 (3.2%) patients, and 7 events of insomnia were reported by 5 (2%) patients (Table 3). No deaths were reported throughout the study.

Efficacy Evaluation

The percentage of patients achieving plasma HIV-1 RNA < 50 copies/mL at week 24 was 86.8% (FAS), 89.1% (FAS complete cases), and 88.6% (PPS) (Figure 3). When the missing data from FAS was imputed with log₁₀ transformed value of 1, the mean ± SD plasma HIV-1 viral load showed 3.8 ± 1.77 and 1.3 ± 1.03 at baseline and at week 24, respectively, with a change from the base line value of 2.4 (SD, 1.95). Similar results were recorded for the PP set. The CD4 cell count showed marked improvements with an increase from 350.2 (SD, 239.73) at baseline to 494.6 (SD, 261.40) at week 24 with an average increase of 143.2 (SD, 226.14) cells. The proportion of patients with virological response were similar across FAS and PP [134.9 (SD-214.96) cells] sets for the CD4 cell count.

Table 3 Summary of Treatment Emergent Adverse Events by SOC and PT [$> 2\%$ Patients] - Safety Set

System Organ Class Preferred Term	Dolutegravir 50 mg (N=250)	
	Number of Events	Subjects n (%)
Number of Subjects with at least one AE	389	144 (57.6%)
Blood and lymphatic system disorders	7	6 (2.4%)
Anemia	5	5 (2.0%)
Gastrointestinal disorders	74	39 (15.6%)
Diarrhea	8	6 (2.4%)
Hyperchlorhydria	11	8 (3.2%)
Nausea	8	8 (3.2%)
Vomiting	23	16 (6.4%)
General disorders and administration site conditions	76	58 (23.2%)
Fatigue	12	11 (4.4%)
Pain	20	16 (6.4%)
Pyrexia	40	35 (14.0%)
Infections and infestations	58	38 (15.2%)
Nasopharyngitis	14	14 (5.6%)
Upper respiratory tract infection	22	15 (6.0%)
Urinary tract infection	9	7 (2.8%)
Investigations	8	8 (3.2%)
Metabolism and nutrition disorders	7	6 (2.4%)
Musculoskeletal and connective tissue disorders	23	7 (2.8%)
Nervous system disorders	73	54 (21.6%)
Dizziness	9	8 (3.2%)
Headache	59	45 (18.0%)
Psychiatric disorders	10	7 (2.8%)
Insomnia	7	5 (2.0%)
Respiratory, thoracic, and mediastinal disorders	13	9 (3.6%)
Cough	8	8 (3.2%)
Skin and subcutaneous tissue disorders	30	20 (8.0%)
Rash	10	8 (3.2%)

Abbreviations: AE, adverse events; PT, preferred items; SOC, system organ class.

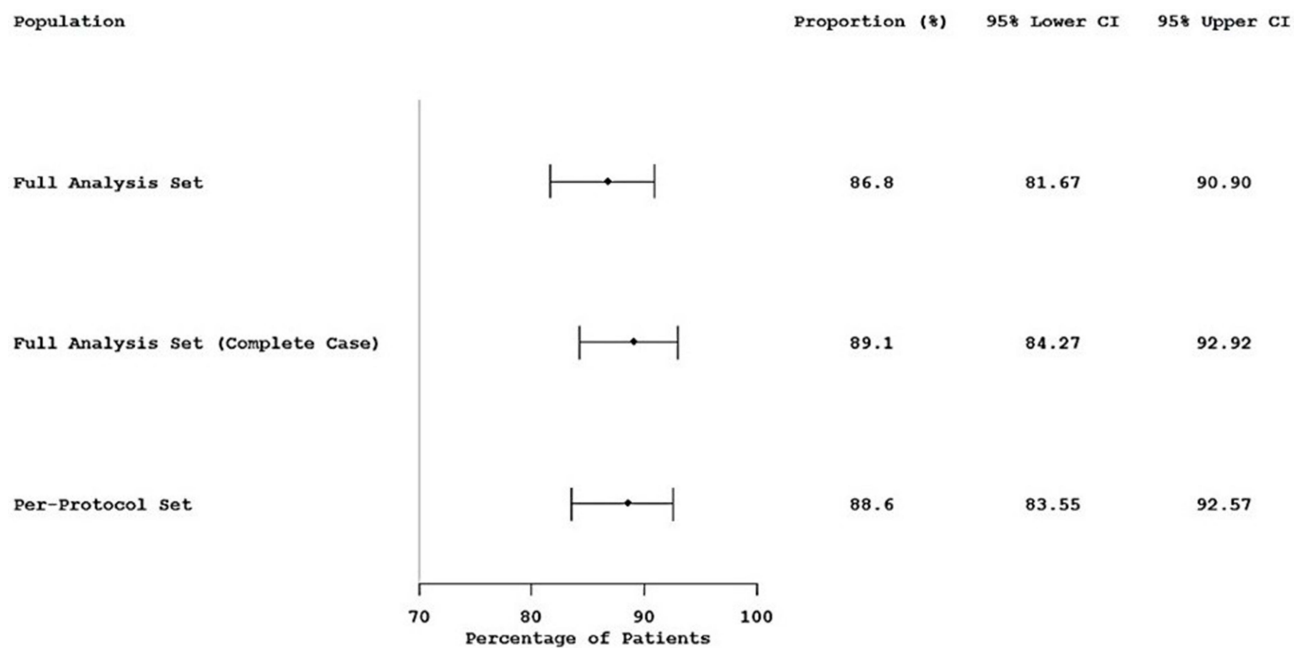


Figure 3 Forest plot for the proportion and confidence interval (95% CI) for efficacy responders.

Discussion

In this study, the safety, tolerability and efficacy of DTG (50 mg once daily) given along with TDF and 3TC, in treatment naïve adult Indian patients living with HIV-1 was evaluated.

We found that majority of the AEs reported were of mild or moderate severity; however, one severe AE was reported in the form of Anemia. A single SAE (0.4%, pyrexia) was reported in one patient, which was comparable to FLAMINGO study.²⁴ The event was unrelated to the study drug, resolved within three days and the patient continued and completed the study. One TEAE (0.4%) of “decreased creatinine clearance” led to drug discontinuation of a single patient. This is in line with other studies^{24–27} signifying lower or comparable proportions of discontinuation with DTG compared to EVF [3% vs 11%], bictegravir [2% vs 2%], darunavir [2% vs 4%] and raltegravir [2% vs 2%]. Some of the common AEs observed in this study include headache, pyrexia, vomiting, upper respiratory tract infection and rash. These observations were in line with other published literature,^{24,27–29} reference safety information and product label. Very few events of sleep disturbance and no events of weight gain were seen, though such reports have been widely observed previously.^{12,30–34} No clinically significant abnormalities in vital signs, laboratory assessments and physical examination from baseline were reported during the study period. This is consistent with a DTG study conducted previously in the Indian population.³⁵

Efficacy analysis showed that 86.8% of patients achieved efficacy endpoint of HIV-1 RNA load < 50 copies per mL by week 24. Results were consistent with FAS and PPS. Our findings are similar to Phase 3 reports of FLAMINGO (90%) and SPRING-2 studies (88%); however, different combinations of ARV drugs were studied in these trials [FLAMINGO: DTG 50 mg or Darunavir 800mg + Ritonavir 100mg vs Tenofovir-Emtricitabine or Abacavir-Lamivudine; SPRING-2: DTG 50 mg or Raltegravir 400mg vs Tenofovir-Emtricitabine or Abacavir-Lamivudine] with end points measured at week 48 and week 96 as against to week 24 in our study.^{24,27} Furthermore, the immunological response to the treatment was observed by a mean increase in CD4+ count by 143.2 cells from baseline to week 24 as seen in previous studies^{24,27} gives the advantage for the physician to use DTG based regimens as the first option of treatment. These observations can be attributed to a high percentage of treatment compliance (96.6%).

A recent NMA evaluating the safety and efficacy of DTG over low dose EFV concluded that DTG has significantly higher odds of viral suppression rates (OR: 1.64; 95% CI: 1.35–1.96 at 48 weeks), more effective in increasing the CD4

cell count, lower rates of drug resistance¹¹ and less neuropsychiatric AEs.^{11,36} In another study³⁷ comparing EFV and DTG clinical outcomes, DTG had a better survival rate at 2 years (90.2% vs 86.7%) and 5 years (83.0% vs 76.7%), higher life expectancy (24.8 years vs 22.0 years and better compliance (99.2% vs 97.9%).

National AIDS control organization (NACO) of India is focused on achieving the ‘End of AIDS’ by 2030. To achieve this, it has adopted Joint United Nations Programme on HIV and AIDS (UNAIDS) 90–90–90 plan where 90% of people living with HIV/AIDS (PLHA) know their HIV status; 90% who know their status are on ART; and 90% on ART have suppressed viral load.³⁸ However, India has not achieved the target despite good improvement in the year 2019–2020 compared to year 2018–2019. Currently, 76% of PLHA know their HIV status, 84% are on ARV and 84% have suppressed viral load.³⁹ Considering the roll out of safer, efficacious, and cost saving³⁷ DTG generic regimen,⁴⁰ India is focused and committed to achieve its target by 2030. Furthermore, implementing DTG as first-line anti-retroviral regimen (instead of EFV, current first-line regimen) will reduce transmission rates and deaths related to HIV/AIDS. Nonetheless, the study has few limitations. This was a single arm open label study. Also, the study was not powered to detect rare AEs with very low incidence. We also excluded pregnant women and hence, we cannot comment on the safety of DTG in pregnancy.

Conclusion

This study demonstrated the safety, efficacy, and tolerability of Dolutegravir 50 mg administered along with fixed dose combination of Tenofovir and Lamivudine among treatment naïve patients living with HIV-1. Our study results support using DTG as the first-line standard of care for treatment naïve patients living with HIV-1 in Indian population.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. However, data sharing will be governed by the company confidentiality policies of Mylan Laboratories Limited, India.

Ethics Approval and Consent to Participate

The study protocol, informed consent and any other written information regarding this study was submitted and approved by the respective independent ethics committees (IEC) and/or institutional review boards of the 14 investigation sites. The details of the IEC and/or institutional review boards is provided in the [Supplementary File 3](#). A written informed consent in compliance with regulatory authority regulations was obtained from each subject before entering the study or performing any unusual or non-routine procedure that involves risk to the subject.

Consent for Publication

This publication contains aggregate data from the clinical trial. No specific subject level information has been included.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

AD has received financial grants for conducting clinical research from Cipla, Mylan, Emcure and MSD pharma private limited and received fees for being speaker at pharma sponsored seminars and webinars organized by Cipla, Mylan, Emcure, MSD, Genex and Aurobindo pharma private limited. SH is an employee of Viartis, Bangalore, India. All other authors have no competing interests to declare in this work.

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