Original Article

Virological outcome and frequency of low-level viremia in patients receiving generic dolutegravir-containing regimen at a large tertiary care clinic in Western India

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Abstract

Background: Dolutegravir (DTG) is widely used for the management of naïve and treatment-experienced HIV-infected patients. Low-level viremia (LLV) is common in patients receiving nonnucleoside reverse transcriptase inhibitor- and protease inhibitor-containing regimens. However, the incidence of LLV associated with DTG-containing regimen is not well known. **Objective:** The objective of this study was to assess the virological response associated with DTG-containing regimens and explored frequencies of LLV and risk factors for the same. **Methods:** We performed a retrospective cohort study of HIV-infected patients receiving generic DTG-containing regimen from February 2017 to July 2019. All adult patients (≥18 years), who completed at least the first follow-up after initiating treatment, were included in this study. LLV was defined as plasma viral load between 20 and 200 copies/ml. **Results:** A total of 597 patients started DTG-containing regimen during the study period, of which 522 patients met the inclusion criteria. The study patients were categorized into five groups: naïve (n = 86), first-line failure (n = 32), second-line failure (n = 53), switch (n = 325), and HIV-2 (n = 26). Complete virological suppression at 6, 12, and 18 months was achieved in 78.5%, 81.1%, and 70.9% of the patients, respectively. Furthermore, 17.9%, 12.9%, and 23.3% of the patients had LLV at 6, 12, and 18 months, respectively. Persistent LLV was found in 2.9% of the patients. Overall, DTG was well tolerated and was discontinued in only three patients due to neuropsychiatric side effects. **Conclusion:** DTG is well tolerated and effective in suppressing HIV across all antiretroviral treatment categories. The rate of persistent LLV is low in DTG-containing therapy.

Key words: Antiretroviral therapy, dolutegravir, generic dolutegravir, India, low-level viremia

INTRODUCTION

Dolutegravir (DTG)-containing regimen is universally recommended for the management of HIV-infected patients by all current clinical practice guidelines.

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The efficacy of DTG has been evaluated in multiple clinical trials for the management of naïve as well as treatment-experienced patients with viral suppression rates varying between 71% and 88%.[1-5] A real-world study from Italy reported a treatment failure rate of 5.4% in a cohort of patients receiving DTG-containing treatment.[6] Two-drug combination therapy which consists of DTG in combination with lamivudine (3TC) had similar efficacy as the triple-drug combination for the treatment of HIV infection.[7] Apart from recommended first-line therapy, DTG is also widely used in patients failing first- and second-line antiretroviral treatment (ART) in India.[8] DTG containing regimen has several advantages compared to ritonavir-boosted protease inhibitors (PI/r) containing ART regimen, which includes, lower cost, small pill size, ease of administration (once a day), potency with a high genetic barrier and better tolerated with a favorable side effect profile. All these factors are also associated with better treatment adherence. Patients receiving stable atazanavir/ritonavir (ATV/r)- or lopinavir/ritonavir (LPV/r)-containing regimen are offered a switch to DTG-containing regimen to simplify ART regimen in India.[8]

Treatment failure is defined as two consecutive viral load (VL) >200 performed at 6–8 weeks' intervals by the US Department of Health and Human Services treatment guideline. On the other hand, the WHO uses a cutoff of 1000 copies/ml to define treatment failure. Many patients receiving ART experience either transient or persistent low-level viremia (LLV), which may be defined as HIV-1 RNA detection at a level ranging from 20 to a few hundred copies/ml. Approximately 20% of the patients receiving suppressive ART can have a transient detectable virus which may become undetectable with the continuation of the same ART, defined as a "blip."[9] Clinical significance and treatment of such transient LLV is not well understood and controversial.[10] Findings from several studies show that LLV may not have an impact on the overall treatment efficacy. However, results from other studies recognize persistent and progressive LLV as a marker of future treatment failure.[11-13] Other potential significant consequences of LLV could be the risk of emergence of drug resistance and persistent immune activation and inflammation.[14,15] A large cohort study from South Africa reported the LLV incidence of 13.59% in patients receiving first-line ART and 13.94% in patients receiving PI/r-containing second-line ART.[16] Other studies have reported higher frequencies of LLV in PI/r-containing regimen compared to nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen.[17] Evidence on frequency of LLV in patients receiving DTG-containing regimen is sparse. Accordingly, the goal of this is to describe the virological outcome and incidence of LLV in patients receiving DTG-containing ART.

Objectives

The primary objective of our study was to determine the virological outcome and incidence of LLV associated with the use of DTG-containing regimen. The secondary objectives were (i) to assess the associated possible risk factors for LLV, (ii) effectiveness of DTG in achieving virological suppression in first- and second-line failure patients, and (iii) maintaining virological suppression in switch patients.

METHODS

We performed a retrospective cohort study of HIV-infected patients receiving DTG-containing regimens between February 2017 and July 2019 at a large tertiary care outpatient clinic in the western region of India. All adult patients (≥18 years) receiving DTG-containing ART, who completed at least the first follow-up with CD4 and/or VL assessment at 3 or 6 months, were eligible for inclusion.

NRTI selection: Treatment naïve patients received tenofovir disoproxylfumerate/emtricitabine (TDF/FTC) or tenofovir alafinamide/emtricitabine (TAF/FTC). All switch patients continued to receive the same NRTI as their previous regimen. NRTI selection was based upon previous NRTI exposures and it's associated toxicities for patients with first and secondline treatment failure.

Patient assessment

The VL testing was performed at 3 and 6 months followed by every 6 months after initiation of ART for all treatment-naïve patients and patients failing first- and second-line ART. The VL assessment in virologically suppressed switch patients was performed every 6 months. Only CD4 cell counts were assessed for all HIV-2 patients. Routine blood and biochemical testing for renal function and lipid profile was performed every 6 months. CD4 testing was not routinely performed for patients with CD4 >350/mm^3 with suppressed VL. Physical examination and any symptoms were recorded. Clinical assessment and treatment adherence counseling were part standard of care and performed at every visit for all patients. Treatment adherence was assessed by patient self-report at each follow-up visit.

Laboratory methods

Plasma VL (pVL) monitoring was performed on ethylenediaminetetraacetic acid plasma samples using Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 version 2.0 (Roche Molecular Systems, Inc., Pleasanton, CA, USA) fully automated real-time polymerase chain reaction with lower limit of detection at <20 copies/ml and quantification range of 20–10,000,000 copies/mL. HIV VL testing was performed three times a week in the laboratory, according to the manufacturer's instructions. Positive results below the lower limit of quantitation of 20 copies/mL were reported as "detected, <20 copies/mL." Target not detected is reported when the machine did not detect a target from a plasma sample.

Outcome definitions

Patients with pVL either <20 copies/ml or target not detected were classified as treatment responders. Patients with isolated low-level VL between 20 and 200 copies/ml which preceded or followed by virologic suppression were classified as transient LLV. Patients with a VL of 201–1000 were classified as high-level viremia (HLV). Patients with two consecutive VL >1000 were classified as treatment failure. Patients with two or more consecutive VL between 20 and 200 were classified as persistent LLV.

Statistical methods

Patient and treatment characteristics were summarized as mean and standard deviation for continuous variables and as rates for categorical variables. The unadjusted and adjusted associations between categorical variables were assessed using the binary logistic regression and summarized as odds ratio along with 95% confidence intervals. The difference in continuous variables across compared groups was assessed using one-way ANOVA and summarized as mean difference along with 95% confidence intervals. To adjust for multiple comparisons, Bonferroni correction was applied. The statistical significance was set at 5% for all comparisons. All data analysis was performed using the IBM SPSS statistical analysis software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA: IBM Corp.)

RESULTS

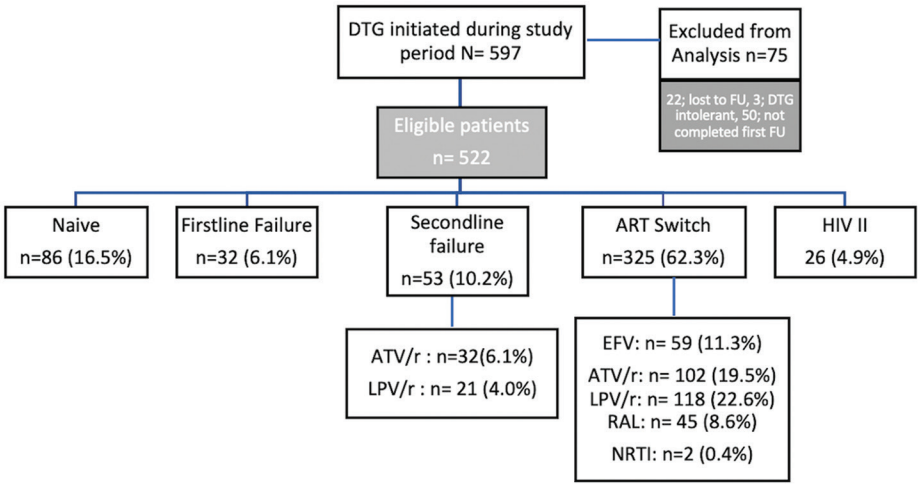
A total of 597 patients were initiated on DTG-containing regimen during the study period, of which 522 patients met the predetermined inclusion criteria. Seventy-five patients were excluded from the analysis, of which 50 patients did not complete the first virological evaluation, 22 were lost to follow-up after initiating ART, and 3 patients discontinued DTG due to neuropsychiatric adverse drug reactions. The flow diagram depicting the patient selection process is shown in Figure 1. The baseline demographic features are shown in Table 1. Patients initiated on DTG-containing ART were categorized into five groups of treatment naïve (n = 86), first-line failure (n = 32), second-line failure (n = 53), switch (n = 325), and HIV-2 (n = 26). Switch category includes patients who were switched from PI/r ATV/r: n = 102, LPV/r: n = 118, efavirenz (EFV): n = 59, and raltegravir (RAL): n = 45. Two patients with NRTI intolerance were switched to DTG + PI/r. TDF/FTC (67.8%) was the most common background NRTI used in DTG-containing regimen followed by zidovudine (AZT)/3TC (7.5%), NRTI + PI/r (6.3%), TAF/FTC (6.3%), AZT/TDF/FTC (4.6%), PI/r (2.9%), and abacavir (ABC)/3TC (4.2%).

Figures 2 and 3 describe virological response with number of patients with VL <20, LLV, HLV, and patients with VL >1000 at each time point in all patients [Figure 2] and various DTG categories [Figure 3]. Overall, 78.5% of the patients achieved fully suppressed pVL at 6 months, 17.9% had LLV, and 2.5% had HLV [Figure 2]. The majority of the patients (97.1%) who had LLV and HLV had transient viremia, while 2.9% had persistent LLV. As illustrated in Figure 2, the proportion of patients with LLV in the naïve, first-line failure, and second-line failure groups was similar. In the switch category [Figure 2], 58 (19.3%) and 23 (7.7%) patients had baseline LLV and HLV, respectively, at the time of switch. A repeat VL assessment at 3 months showed that 39 (50.6%)

Table 1: Baseline demographic features

Baseline characteristics	(n=522)
Age (years); median (range)	48 (18-85)
Weight (kg); median (range)	63 (30-110)
Sex, n (%)	
Male	347 (66.5)
Female	175 (33.5)
CD4/mm^3 (n)	Mean (SD)
Naïve (80)	351.94 (296.59)
First-line failure (22)	115.77 (113.40)
Second-line failure (26)	247.12 (238.92)
Switch patients (54)	296.13 (239.85)
HIV-2 (26)	625.81 (328.77)
Baseline VL (n)	Mean (SD)
Naïve (32)	6.13 $\log_{10}$ (6.56 $\log_{10}$)
First-line failure (27)	5.55 $\log_{10}$ (5.88 $\log_{10}$)
Second-line failure (40)	5.54 $\log_{10}$ (5.88 $\log_{10}$)
Switch patients (300)	1.66 $\log_{10}$ (2.09 $\log_{10}$)

SD=Standard deviation; VL=Viral load



Abbreviations: ATV/r: Atazanavir/ritonavir containing regimen, LPV/r: Lopinavir/ritonavir containing regimen, EFV: Efavirenz containing regimen, RAL: Raltegravir containing regimen, NNRTI: Nucleoside reverse transcriptase inhibitors

Figure 1: Flowchart of study patients

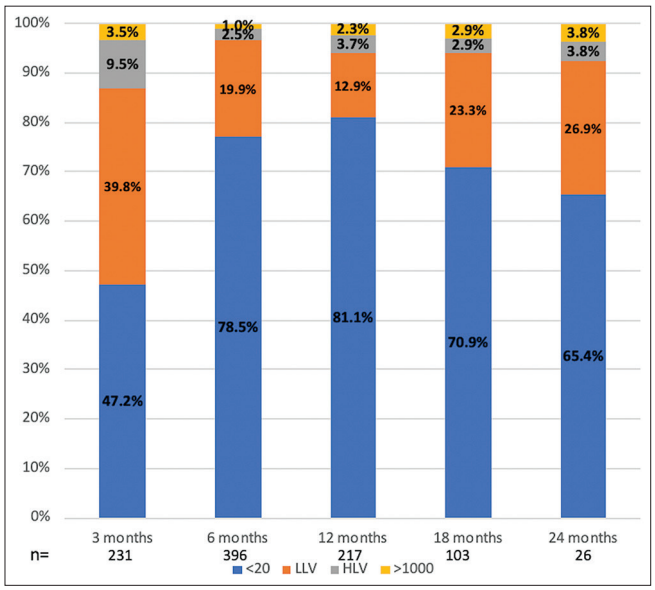


Figure 2: Virological response in all patients

patients who had detectable virus (LLV and HLV) at baseline achieved complete viral suppression and 31 (40.3%) continued to have LLV. At 6 months, 83.1% of the patients achieved complete suppression which was maintained at 12-month follow-up. In the current study, CD4 response is difficult to determine as CD4 testing was not routinely performed in patients with suppressed VL with CD4 count more than 350/cmm. CD4 count response at different time intervals is shown in Figure 4.

The findings from the logistic regression analysis (unadjusted and adjusted for age, gender, weight, baseline VL [>100,000 copies/ml], and background treatment) did not show a statistically significant association between incidence of persistent LLV viremia and ART categories, for example, naïve, first-line failure, second-line failure, and switch patients [Table 2].

Overall, DTG was well tolerated except in three patients where DTG was discontinued due to neuropsychiatric side effects. No significant clinical events were observed during follow-up in patients receiving DTG-containing treatment.

DISCUSSION

The findings from a real-world observational study showed that DTG-containing ART regimen is well tolerated with only 0.57% treatment discontinuation due to neuropsychiatric adverse drug reactions and is associated with virological suppression in the majority (78.5%) of the patients at 6 months which is comparable to previously published DTG studies.[1-3,5] Complete viral suppression reported at 6 months in different DTG ART categories was 76.7% in treatment-naïve, 57.1% in first-line failure, 59.5% in second-line failure, and 83.1% in switch patients. Previous treatment failure and ART exposure had no impact on virological response to DTG-containing therapy in the treatment-experienced patients in our study, despite the fact that 30.2% of the patients received recycled previous background regimen (TDF/FTC) while 24.5% and 9.4% of the patients received TDF/FTC/darunavir (DRV)/r and DRV/r and 13.2% received AZT/TDF/FTC as a background regimen. Results from previous and our real-life studies substantiate that DTG-containing

Table 2: Unadjusted and adjusted (adjusted for age, gender, weight, background treatment, and viral load at baseline) logistic regression analysis of association between antiretroviral treatment type and viremia

ART category	Unadjusted odds ratio	95% confidence intervals	P	Adjusted odds ratio	95% confidence intervals	P
Treatment naive	Reference			Reference		
First-line failure	0.82	0.08-8.16	0.86	1.28	0.06-28.32	0.88
Second-line failure	3.3	0.79-13.86	0.1	2.82	0.19-41.80	0.45
Switch	0.32	0.07-1.47	0.14	0.44	0.03-7.26	0.57

ART=Antiretroviral treatment

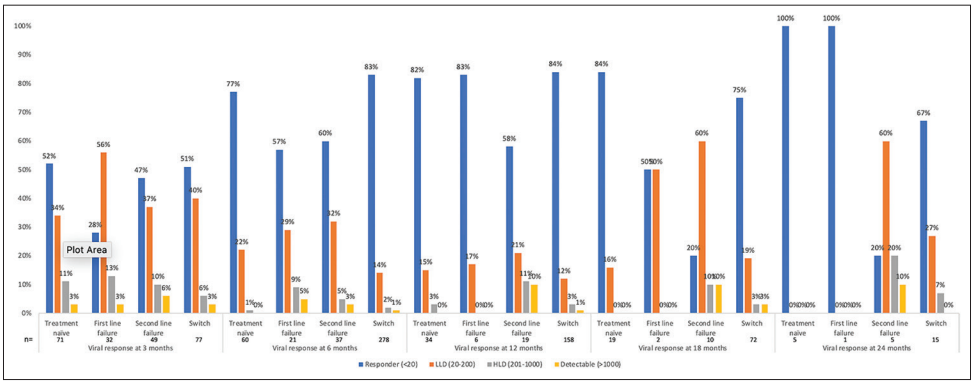


Figure 3: Virological response in antiretroviral therapy categories

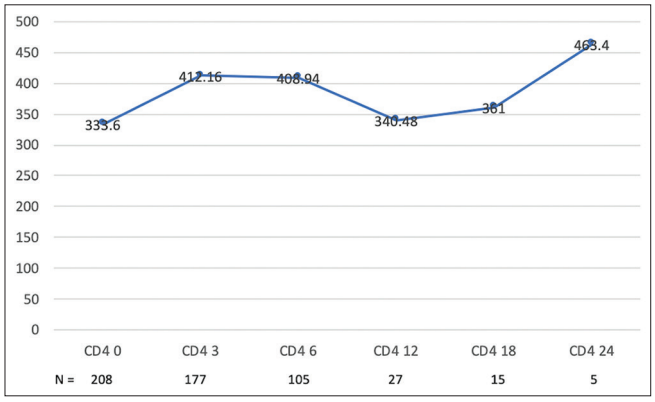


Figure 4: CD4 response in all patients

treatment is robust and effective in patients who experienced and failed previous NNRTI and PI/r-containing ART treatment.[5] None of the previous studies have described the incidence of LLV in patients receiving DTG-containing regimen. The results from our study showed that overall 17.9%, 12.9%, 23.3%, and 26.9% of the patients at 6, 12, 18, and 24 months had LLV. The incidence of LLV at 6 months was 14.4% in switch patients, 32.4% in second-line failure patients, 28.6% in first-line failure patients, and 21.7% in naïve patients. The majority of the patients (97.1%) with LLV had transient LLV, while 2.9% of the patients receiving DTG-containing regimen had a persistent LLV. Palmer *et al*. described residual viremia with low-level replication (1–10 copies/ml) in patients who achieved virologic suppression of <50 copies/ml.[18] Transient detectable viremia on ART is seen in up to 20% of the patients receiving suppressive ART and 4%–10% experience persistent low-level detectable viremia.[9,15,19] Results from the Gemini sudy presented by Mark underwood and colleagues at the 2019 IAS conference reported low level viremia in 14% of patients receiving DTG/3TC and DTG/TDF/FTC arm and persistent LLV was found in 2% of patients in DTG/3TC arm while 1% in DTG/TDF/FTC arm.[20] A higher percentage of patients in our study with transient and persistent LLV are likely to be associated with heterogeneous study population with 16.3% of the patients with first- and second-line treatment failure with high baseline VL and high possibility of harboring baseline NRTI mutations. Other studies with DTG-containing ART reported four patients who had a brief LLV while receiving two-drug combination treatment DTG plus lamivudine, and another study had only one patient with LLV at week 24.[21,22] Another DTG study comparing ABC/3TC/DTG with TDF/FTC/EFV in treatment-naïve patients reported that 74.36% of the patients who failed treatment in DTG arm had LLV (pVL <200 copies/ml).[23]

The impact of LLV on clinical outcomes remains debatable, especially in patients with LLV between 50 and 200 copies/ml. The study favors a low risk of future virologic failure in patients with transient LLV,[14,24] while persistent LLV is associated with future virological failure in other studies.[11,17,25]

Bernal *et al*. reported clinical progression and death in patients who are keeping LLV between 200 and 499 copies/ml.[13] A recent study by Fleming *et al*. supported the future risk of treatment failure in patients with VL between 200 and 500 copies/ml and reported a higher risk of treatment failure in treatment-experienced patients with VL between 50 and 200 copies/ml.[26] Immune activation is another negative health consequence reported in patients keeping LLV.[27] A study from Geretti *et al*. describes that LLV (50–400 copies/ml) occurred in 25.5% of the patients during the 1st year on ART, and LLV is less likely to occur in patients receiving NRTI plus NNRTI-containing therapy compared to other regimens including triple NRTI.[17] Calcagno *et al*. reported that patients receiving both NNRTI-containing and RAL-containing regimens had the highest prevalence of target not detected as compared to PI/r-containing regimen.[11] Our study had a heterogeneous group of patients, including treatment naïve, and treatment-experienced patients showed an overall similar incidence of transient LLV compared to study from Geretti *et al*. with treatment-naïve populations.[17] Very high baseline VL, shorter duration of ART, and presence of baseline resistance mutation are identified as important risk factors for LLV in a French study in addition to antiretroviral agents used for the treatment and missing dosages.[17,28] In our cohort, logistic regression analysis did not show an association between baseline VL, previous treatment failure, and background regimen on persistent detectable viremia. In the current study, patients had a high mean VL of 5.55 $\log_{10}$ and 5.54 $\log_{10,}$ respectively, in the categories of the first- and second-line failure groups. Despite this late diagnosis in the treatment-experienced patients, virological suppression and LLV are comparable to naïve and switch category patients. Self-reported adherence in our study is relied upon as virological outcome is at par with previous findings.[2-5] In our cohort, VL test was carried out by fully automated AmpliPrep/TaqMan system assay, and this can result in a twofold increase in the patients experiencing LLV who were suppressed with <50 copies/ml.[29] Preexisting resistant drug mutation for NRTIs and PIs in our patients in the first- and second-line failure groups might also be contributing to higher transient LLV in the current study. Generic drug used in this cohort may not be a reason for LLV in our cohort as nearly 80% of the patients achieved viral suppression at 6 months of treatment, which is matching with previous DTG studies. The key limitations of our study include observations from a single-center study. Furthermore, the follow-up duration varied across the patient population, thereby affecting the long-term outcomes which are needed for assessment of persistent LLV. However, these above mentioned limitations are always associated with observational studies and are reflective of a real-world setting.

CONCLUSION

Overall, our real-life retrospective study supports the use of DTG-containing regimen to treat HIV-infected patients across all ART categories: treatment-naïve, first- and second-line treatment failure, and switching regimens in patients receiving suppressive ART regimens with good virological suppression. DTG is better tolerated with very few discontinuation rates due to adverse drug reactions. Clinicians should carefully monitor patients for LLV, especially persistent LLV, for future treatment failure.

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Conflicts of interest

Sanjay Pujari received speaker fees from Emcure Pharmaceuticals company and the rest of the authors disclose no conflict of interest.

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