Safety, Tolerability, and Efficacy of Generic Dolutegravir-containing Antiretroviral Therapy Regimens Among South Indian Human Immunodeficiency Virus-infected Patients

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In this first study of generic dolutegravir (DTG)-containing regimens in a low-resource setting, we assessed safety, tolerability, and efficacy within a prospective cohort of 564 patients with at least 6 months of clinical follow-up. We provide support for a large-scale transition to DTG as part of first-line regimens.

Keywords. HIV; dolutegravir; safety; efficacy; resource-limited setting.

The use of dolutegravir (DTG)-based antiretroviral therapy (ART) is now the standard of care in high-resource settings. The World Health Organization (WHO) recommended DTG-containing ART regimens as alternatives in their 2016 ART guidelines and issued new guidance to move toward ART regimens that do not use nonnucleoside reverse transcriptase inhibitors (NNRTIs), which are preferred in regions with $\geq 10\%$ baseline NNRTI resistance [1]. Despite DTG having an improved adverse effect (AE) profile and high genetic barrier to developing resistance, widespread implementation in low-resource settings is lagging [2]. Barriers include cost and initial clinical studies on DTG that excluded pregnant women (and included only 16% women) [3]. Recent concerns about neural tube defects among newborns born to women using DTG at the time of conception further emphasize the need for more data [4]. We sought to assess the safety, tolerability, and efficacy of generic DTG-based regimens among patients in a low-resource setting.

METHODS

Since 1996, the YRG Centre for AIDS Research and Education (YRGCARE Medical Centre)-VHS, Chennai, India, a non-profit

medical and research institution, has provided holistic care for over more than 23 000 persons with human immunodeficiency virus (HIV) infection. Patients are treated according to WHO guidelines. Generic DTG was introduced in India in April 2017. Since then, 564 persons have received DTG-based regimens. Demographics and characteristics are shown in Table 1.

The following 6 groups of patients aged >18 years were included for this analysis: treatment-naïve ($N = 137$), under-going first-line substitution from NNRTI-containing ART ($n = 145$), failed NNRTI-containing first-line ART and switched to DTG in second-line regimen ($N = 40$), underwent substitution from a tenofovir (TDF) plus lamivudine (3TC) or emtricitabine (FTC) plus ritonavir boosted protease inhibitor (PI)-containing second-line regimen ($N = 100$), were on a DTG+ PI-containing alternate second-line regimen ($N = 78$), and either failed second-line regimen or underwent substitution to a DTG-containing a third-line regimen ($N = 64$). This study included patients with at least 6 months of clinical follow-up ($N = 239$); 72 had 12 months of clinical follow-up. A subgroup analysis of those patients on double-dose DTG-based ART and anti-tuberculosis therapy (ATT) was also performed.

Analyses were carried out using the YRGCARE Chennai HIV Observational Database, which is updated daily and collects demographic, clinical assessment, and laboratory data [5]. Per WHO guidelines, patients in follow-up received laboratory monitoring of CD4 cell counts at least every 6 months after initiating therapy and plasma HIV viral RNA monitoring (PVL) at least every 12 months. Creatinine and liver enzymes were measured at baseline, 1 and 6 months after ART initiation, and every 6 months thereafter.

Descriptive statistics were calculated with mean and standard deviation for normally distributed variables and with median and interquartile range (IQR) for those influenced by extreme values. Statistical analyses were performed with SPSS (version 22.0; SPSS, Chicago, IL).

RESULTS

Between April 2017 and May 2018, 564 patients initiated DTG-containing ART. Total follow-up was 276.1 person-years; 239 (42.3%) had ≥ 6 months of clinical follow-up and 72 (12.7%) had ≥ 12 months of clinical follow-up. Two-thirds (66.7%) were male; at the time of DTG initiation, median age was 43.1 years and median body mass index was 24.8 kg/m^2 (IQR, 22.2–27.4). Of those who underwent ART substitution, the most common first-line regimen was TDF plus 3TC plus efavirenz (EFV) (75%); TDF plus 3TC plus ritonavir-boosted atazanavir (28.1%) and darunavir plus raltegravir plus ritonavir (25%) were the most common second- and third-line regimens, respectively.

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Table 1. Baseline Characteristics by Treatment Group and 6-Month Follow-up Values

	First-line Therapy (N = 282)			Second-line Therapy (N = 218)			Third-line Therapy (N = 64)
	TDF+3TC/FTC+DTG (Treatment Naïve) (N = 137)	TDF+3TC/FTC+DTG (First-line Substitution) (N = 145)	TDF+3TC/FTC+DTG (First-line Switch) (N = 40)	TDF+3TC/FTC+DTG (Second-line Substitution) (N = 100)	DTG+ATVr/ LPVr (Second-line Substitution) (N = 78)	DTG+DRVr (Second-line Switch/ Third-line Substitution)	
Characteristic, N (%), Median (Interquartile Range)	Total (N = 564)						
At the time of DTG initiation							
Female	188 (33.3)	48 (35.0)	50 (34.2)	17 (42.5)	25 (32.1)	11 (17.2)	
Median age	43.1 (35.4, 50)	38 (30, 46.2)	42 (35.1, 48.2)	41 (35.4, 47)	45.4 (38.7, 51)	46.4 (41.3, 51.9)	
Body mass index (kg/m ²)	24.8 (22.2, 27.4)	25.6 (21.4, 27.6)	24.3 (20.9, 26.5)	29.6 (22.9, 31.8)	25.6 (19.8, 29.3)	18.9 (18, 25)	
CD4 cell count	432 (236, 647)	477 (263, 578)	558 (377, 767)	276 (167, 533)	203 (140, 505)	109 (37, 309)	
Viral load ^a	96 (40, 20400)	14791 (2840, 35700)	<40 (<40, <40)	1399 (66, 366804)	435 (48, 30290)	127939 (680, 768384)	
Hemoglobin	12.3 (10.3, 13.8)	12.7 (10.1, 13.4)	13.1 (11.5, 13.8)	11.9 (10.1, 13.5)	10.2 (8.6, 13.6)	11.8 (10.8, 13.0)	
Total bilirubin	0.68 (0.46, 0.97)	0.66 (0.58, 0.80)	0.62 (0.39, 0.92)	0.45 (0.42, 0.50)	0.98 (0.52, 1.89)	0.7 (0.69, 0.7)	
AST [SGOT]	43 (26, 61)	26 (22, 30)	46 (30, 58)	34 (16, 149)	41 (29, 85)	51 (N/A)	
ALT [SGPT]	26 (18, 55)	25 (17, 46.5)	24.5 (16.5, 63)	22 (15, 55)	25.5 (21, 35.5)	23 (17, 29)	
Creatinine	0.9 (0.7, 1.1)	0.9 (0.8, 1.0)	0.8 (0.7, 0.95)	0.75 (0.7, 0.9)	1.0 (0.75, 1.35)	0.7 (0.6, 0.8)	
At 6 months (N = 239)							
CD4 cell count	413 (197.5, 659.5)	454 (433, 475)	487 (297, 898)	298 (N/A)	222 (168, 204)	385 (144, 744)	
Viral load	123 (<40, 3095)	<40 (<40, <40)	64 (<40, 113)	N/A	1336 (63, 951 218)	86 (<40, 706)	
Hemoglobin	13 (11.8, 13.9)	13.7 (12.1, 14.9)	13.5 (12.3, 14.1)	10.5 (N/A)	10.7 (9.2, 12.3)	13.6 (11.8, 14.2)	
Total bilirubin	0.59 (0.39, 0.97)	0.58 (0.39, 0.71)	0.78 (0.78, 1.14)	0.33 (0.31, 0.34)	0.85 (N/A)	0.43 (0.39, 0.51)	
AST [SGOT]	24 (20.5, 27)	26 (25, 27)	14 (N/A)	20 (N/A)	23 (N/A)	50 (N/A)	
ALT [SGPT]	22 (16, 31)	26.5 (18, 40)	24 (14, 80)	15(12, 18)	16 (N/A)	22 (16, 24)	
Creatinine	1 (0.8, 1.2)	1.1 (0.9, 1.1)	1.0(0.8, 1.1)	0.9 (0.6, 1.2)	1.1 (N/A)	1.1 (0.8, 1.2)	
New diagnosis of noncommunicable diseases ^b	0 (0)	0	0	0	0	0	
Adverse effects ^c	2 (0.8)	0	0	0	1 (2.3)	1 (2.4)	
All-cause mortality	3 (1.3)	0	0	0	1 (2.3)	2 (4.8)	

Abbreviations: 3TC, lamivudine; ALT, alanine transaminase; AST, aspartate transaminase; ATVr, ritonavir-boosted atazanavir; DRVr, ritonavir-boosted darunavir; DTG, dolutegravir; FTC, emtricitabine; LPVr, ritonavir-boosted lopinavir; N/A, not available due to low sample size; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TDF, tenofovir disoproxil fumarate.

^aLower limit of human immunodeficiency virus RNA detection is either <150 copies or <40 copies.

^bIncidence of noncommunicable diseases including hypertension and type II diabetes mellitus.

^cPatient reported anemia, gastroenteropathy, idiopathic thrombocytopenic purpura, hepatitis, or cholecystitis.

Overall, kidney function remained stable at 6 months follow-up, with median creatinine at initiation of 0.9 (IQR, 0.7–1.1), and 1.0 (IQR, 0.8–1.2) and 0.9 (IQR, 0.85–1.1) at 6 and 12 months, respectively. No patients had an increase in liver enzymes as per the National Institutes of Health/Division of Acquired Immuno Deficiency Syndrome grading scale. Overall frequency of opportunistic infections (OIs) decreased from 7.4% prior to starting DTG to 3.3% 6 months later; immune reconstitution inflammatory syndrome, sleep disturbances, and neuropsychiatric symptoms were not reported in this cohort after DTG initiation. No patients discontinued DTG at 6 months; no treatment failures were noted after initiating a DTG-based regimen. Four patients died; case sheet review revealed that no deaths were related to DTG toxicity. Causes of death were sepsis (n = 2) and cytomegalovirus encephalitis (n = 2).

Among treatment-naïve patients, every individual with 6-month follow-up PVL was virally suppressed, with a 100-fold reduction in PVL levels observed. The overall proportion of individuals in all groups who were virally suppressed at the time of DTG initiation was 48.9%; after 6 months, it was 82.9%.

Subgroup analysis of patients (n = 56) on twice-daily DTG plus ATT revealed an increase in median CD4 count and decrease in median PVL at 6 months; no elevation of liver enzymes or creatinine was noted.

Three patients had received DTG while pregnant, with 1 reporting early abortion; the remaining had not yet delivered.

DISCUSSION

DTG is a new and promising integrase strand transfer inhibitor that is part of an ART regimen for both treatment-naïve and experienced individuals. This is the first report on the use of generic DTG-containing ART regimens from a resource-limited setting. The safety and tolerability of DTG-based ART regimens in our cohort of patients initiating generic DTG was very good, with excellent efficacy in suppressing or maintaining the PVL below the detection level.

Treatment-naïve individuals placed on first-line DTG-containing therapy showed stable liver function and a nonsignificant increase in median creatinine at 6 months that stabilized by 12 months. This is consistent with initial studies on DTG [3]. No incidence of liver or kidney dysfunction was noted. The substantial reduction in PVL levels seen here shows the tremendous efficacy of DTG regimens in this cohort. We switched individuals stable on EFV-containing therapy to avoid discontinuation from long-term AEs of EFV therapy. These patients showed stable kidney and liver function and CD4 counts at 6 months, and none reported DTG discontinuation or AEs [6]. Notably, none of the patients in our cohort reported sleep disturbances, though this was noted in a European cohort [7].

Those patients who underwent first-line switch reported no AEs or OIs at 6 months, and all had stable liver and kidney functions. However, we have limited follow-up data to assess

continued virologic suppression at 6 months in this group, and future studies are needed.

WHO guidelines recommend the use of 2 nucleoside RTIs (NRTIs) plus a boosted PI as preferred second-line therapy; however, long-term PI use is associated with increased development of metabolic disorders that may not be entirely reversible [8]. The higher risk of renal dysfunction when taking TDF plus a PI also necessitates routine renal function monitoring [9]. Further, the DAWNING trial showed that 2 NRTIs plus DTG was superior to 2 NRTIs plus a PI for patients failing first-line therapy [10]. For these compelling reasons, DTG was substituted for ritonavir-boosted PIs in 100 patients, all of whom showed better tolerability with no treatment discontinuation. We expect continued virologic suppression in this cohort, but currently have limited follow-up to assess this.

Those patients who were placed on a third-line regimen containing DTG plus ritonavir-boosted darunavir showed increases in CD4 count and decreases in PVL at 6 months. The low prevalence of reported AEs, OIs, and discontinuation suggest that this new regimen is well tolerated, and stable liver and kidney function tests suggest its safety in this group. Neither of the 2 deaths in this group was attributable to DTG therapy.

In our cohort, among patients who were receiving a rifampicin-containing ATT regimen, the DTG dose was doubled as per guidelines to adjust for rifampicin CYP3A4 induction that reduces plasma DTG concentrations [11]. None of these patients developed kidney or liver dysfunction. Viral suppression was seen in individuals who had PVL at 6 months; none discontinued DTG. Our clinical results suggest double-dosing DTG in combination with rifampicin-containing ATT is a safe therapeutic option.

In our cohort, DTG was prescribed to 2 women who were pregnant and 1 who became pregnant. We observed early fetal demise in the latter, but no autopsy was done. While DTG appears safe in pregnancy, its safety in the preconception/early gestation stage remains questionable. Recently in Botswana, 4 cases of neural tube defects were noted among newborns born to women on DTG-based regimens at the time of conception [4]. Future surveillance is needed from programs that use DTG among women of child-bearing age. Recently, guidelines have issued a caution on the usage of DTG among child-bearing women intending to become pregnant [4].

Treatment resistance is a major concern, especially in low-resource settings, but DTG has a higher barrier to developing resistance than existing medications [2]. This, along with the reduced frequency of AEs and excellent efficacy, makes DTG an attractive replacement for EFV in first-line therapies in low-resource settings [12]. Our data show the potential benefits of DTG rollout among ART-naïve and experienced patients; our group has already shown DTG to be cost-effective in low-resource settings [13]. Further research is needed to determine if widespread DTG implementation can have a greater impact on

HIV prevention in the community due to quicker achievement of viral suppression [10, 14].

In conclusion, generic DTG-based ART was safe, well tolerated, and efficacious in our cohort of patients in a low-resource setting. Our data provide support for incorporating DTG regimens as the standard of care in resource-limited settings and call for rollout of large-scale DTG transition programs.

Notes

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