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BRIEF REPORT

Efficacy and Safety of Switching to Dolutegravir/Lamivudine Versus Continuing a Tenofovir Alafenamide–Based Regimen in Virologically Suppressed Adults With Human Immunodeficiency Virus Type 1: Subgroup Analysis of Participants With Elvitegravir as Baseline Third Agent From the TANGO Study

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TANGO results have established the durable efficacy of dolutegravir/lamivudine in virologically suppressed individuals who switched from 3- or 4-drug tenofovir alafenamide (TAF)–based regimens. In this post hoc subgroup analysis, 144-week efficacy and tolerability of dolutegravir/lamivudine in participants who switched from elvitegravir/cobicistat/emtricitabine/TAF were consistent with the overall switch population.

Clinical Trials Registration. NCT03446573.

Keywords. dolutegravir/lamivudine; elvitegravir; HIV-1; switch study; virologically suppressed.

Lifelong treatment with antiretroviral therapy (ART) is required to maintain virologic suppression and extend life expectancy in people with human immunodeficiency virus (HIV) [1, 2]. Due to the need for long-term therapy, antiretroviral agents must maintain efficacy while limiting toxicity [1]. The 2-drug regimen dolutegravir (DTG)/lamivudine (3TC) has demonstrated noninferior efficacy and a good tolerability profile when compared with traditional 3- or 4-drug regimens in phase 3 clinical trials [3–5]. On the basis of these data, DTG/3TC is recommended as a first-line option for HIV type 1 (HIV-1) treatment in individuals without previous ART exposure and in those on a suppressive ART regimen who choose to switch [2, 6, 7].

Results from the TANGO study, in which adults with HIV-1 switched to DTG/3TC from 3- or 4-drug tenofovir alafenamide (TAF)–based regimens, demonstrated that the proportion of participants with HIV-1 RNA ≥50 copies/mL was noninferior compared with those continuing TAF-based regimens through week 144 [4, 8]. The majority of participants in TANGO were using boosted elvitegravir (EVG) as the third agent at baseline [4]. As an integrase strand transfer inhibitor (INSTI), EVG has a mechanism of action similar to that of DTG but requires co-formulation with the pharmacological booster cobicistat, increasing the potential for drug interactions [2]. The objective of this post hoc analysis was to compare long-term efficacy and safety outcomes in TANGO participants who switched to DTG/3TC from an EVG/TAF-based regimen with those who continued their EVG/TAF-based regimen.

METHODS

TANGO (ClinicalTrials.gov identifier NCT03446573) is a randomized, open-label, noninferiority phase 3 study that evaluated efficacy and safety of switching to DTG/3TC versus continuing TAF-based regimens in virologically suppressed adults with HIV-1 [4, 8]. Detailed methods have been published [4, 8]. In brief, adults with virologic suppression (HIV-1 RNA <50 copies/mL) after first-line therapy with a TAF-based regimen for >6 months were randomized 1:1 to switch to once-daily DTG 50 mg/3TC 300 mg fixed-dose combination or continue their current regimen. The primary endpoint was proportion of participants with HIV-1 RNA ≥50 copies/mL (US Food and Drug Administration Snapshot algorithm; intention-to-treat–exposed [ITT-E] population) at week 48. In this post hoc subgroup analysis of participants with EVG as baseline third agent, the primary outcome was proportion with HIV-1 RNA ≥50 copies/mL and <50 copies/mL (Snapshot; ITT-E population) at week 144. Secondary outcomes included change from baseline in $CD4^+$ cell count, weight, and fasting lipids. Incidence of drug-related adverse events (AEs) was also summarized.

All randomized participants who received ≥1 dose of study treatment were included in the ITT-E population and used for efficacy and safety analyses unless incorrect or no study treatment was received. One participant who switched to DTG/3TC had missing 144-week data due to the coronavirus disease 2019 pandemic but was included in the Snapshot analysis. Proportions of participants with HIV-1 RNA ≥50 and

Received 27 November 2023; editorial decision 16 April 2024; published online 2 May 2024
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https://doi.org/10.1093/ofid/ofae227

<50 copies/mL (Snapshot) were summarized. Unadjusted treatment difference for subgroups was calculated by proportion on DTG/3TC – proportion on EVG/TAF-based regimen. Mean change from baseline in $CD4^+$ cell count was assessed for each group. Adjusted mean change from baseline in weight was also assessed for each group. Estimated adjusted ratios (week 144 to baseline) were calculated to compare changes in fasting lipid levels.

Patient Consent Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Study protocols and documents were reviewed and approved by national, regional, or investigational center ethics committees or institutional review boards. All participants provided written informed consent before study initiation.

RESULTS

The TANGO ITT-E population included 741 participants, 369 who switched to DTG/3TC and 372 who continued their TAF-based regimen [4]. Overall, 492 (66%) participants were taking EVG/cobicistat/emtricitabine (FTC)/TAF as their TAF-based regimen at baseline (DTG/3TC, n = 243; TAF-based regimen, n = 249). In the baseline EVG subgroup, demographics were similar between the DTG/3TC and TAF-based regimen groups, respectively: Participants were primarily male (94% and 92%) and aged <50 years (81% and 78%), with 83% and 79% identifying as White, 12% and 16% as Black or African American, 2% and 2% as Asian, and 3% and 4% other races.

At week 144, 209 of 243 (86%) participants in the DTG/3TC group had HIV-1 RNA <50 copies/mL compared with 206 of 249 (83%) in the EVG/TAF-based regimen group (unadjusted treatment difference, 3.3 [95% confidence interval {CI}, −3.1 to 9.7]; Table 1; Supplementary Figure 1), consistent with results from the overall ITT-E population (DTG/3TC, 86% [317/369]; TAF-based regimen; 82% [304/372]) [4]. Proportions of participants with HIV-1 RNA ≥50 copies/mL and those for whom virologic data were not available were similar between the DTG/3TC group (<1% and 14%, respectively) and EVG/TAF-based regimen group (1% and 16%, respectively). No participants in the DTG/3TC group, regardless of baseline regimen, met criteria for confirmed virologic withdrawal (defined as 2 consecutive on-treatment viral loads ≥50 copies/mL, with the second measurement ≥200 copies/mL). Two participants in the EVG/TAF-based regimen group met confirmed virologic withdrawal criteria with no resistance observed.

Mean change in $CD4^+$ cell count from baseline at week 144 was 68.2 (standard deviation [SD], 222.3) cells/μL in the DTG/3TC group and 33.4 (SD, 183.1) cells/μL in the EVG/TAF-based regimen group, which was consistent with results in the overall population (DTG/3TC, 56.2 [SD, 211.6] cells/μL; TAF-based regimen, 31.7 [SD, 174.6] cells/μL) [4].

Table 1. Summary of Efficacy (Snapshot Analysis, Intention-to-Treat–Exposed Population) and Safety Outcomes (Safety Population) at Week 144 in Participants Using an Elvitegravir/Tenofovir Alafenamide–Based Regimen at Baseline

Outcome	EVG/TAF at Baseline	
	DTG/3TC (n = 243)	TAF-Based Regimen (n = 249)
HIV-1 RNA <50 copies/mL	209 (86)	206 (83)
HIV-1 RNA ≥50 copies/mL	1 (<1)[a]	3 (1)[b]
No virologic data	33 (14)	40 (16)
Discontinued due to AE or death	15 (6)	4 (2)
Discontinued for other reasons	17 (7)	36 (14)
On study but missing data in window	1 (<1)	0
Change from baseline in $CD4^+$ cell count, mean (SD), cells/μL	68.2 (222.3)	33.4 (183.1)
Any drug-related AE	35 (14)	13 (5)
Drug-related AEs occurring in ≥1% of either treatment group		
Weight increased	6 (2)	4 (2)
Insomnia	5 (2)	0
Nausea	3 (1)	1 (<1)
Constipation	3 (1)	0
Flatulence	3 (1)	0
Drug-related AEs leading to withdrawal	10 (4)	3 (1)

Data are presented as No. (%) unless otherwise specified.

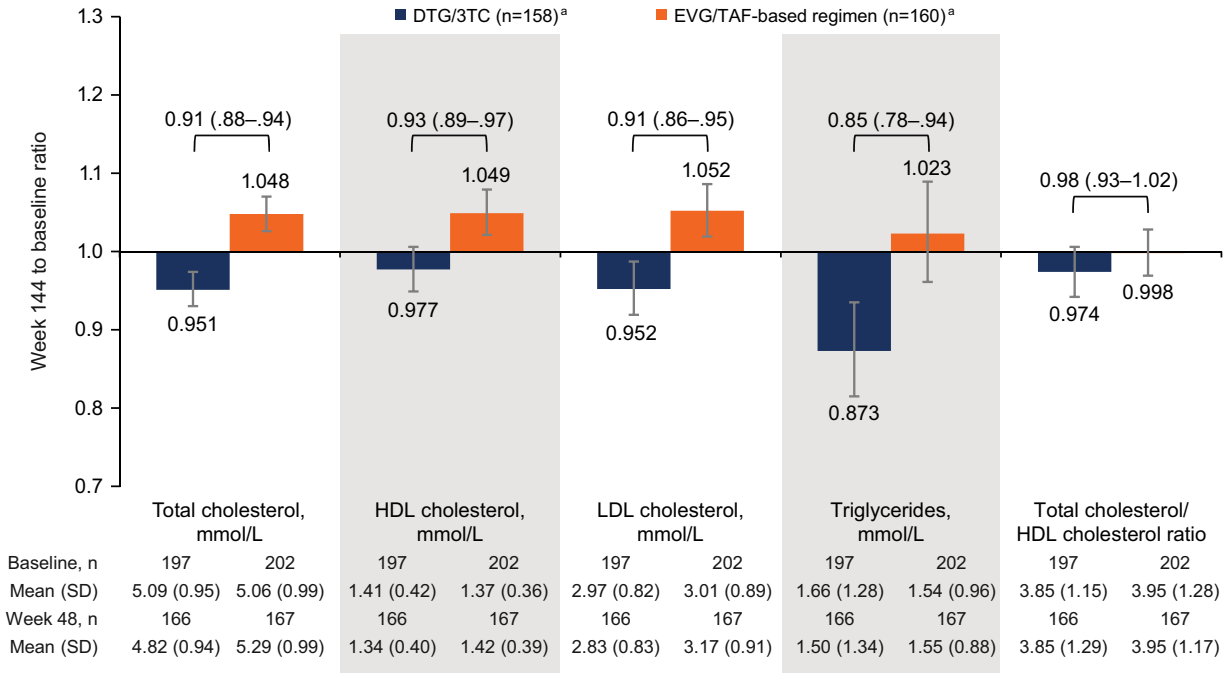
Abbreviations: 3TC, lamivudine; AE, adverse event; DTG, dolutegravir; EVG, elvitegravir; HIV-1, human immunodeficiency virus type 1; ITT-E, intention-to-treat exposed; SD, standard deviation; TAF, tenofovir alafenamide.

[a]Discontinued for other reason and not below threshold.

[b]Discontinued for lack of efficacy.

More participants who switched to DTG/3TC (n = 35 [14%]) experienced drug-related AEs compared with those who continued their EVG/TAF-based regimen (n = 13 [5%]; Table 1), consistent with the overall population (DTG/3TC, 15%; TAF-based regimen, 5%) [4]. The most common drug-related AEs in participants who switched to DTG/3TC were weight gain (n = 6, 2%) and insomnia (n = 5 [2%]; Table 1). The most common drug-related AE in participants continuing their EVG/TAF-based regimen was weight gain (n = 4 [2%]). More participants withdrew from the study because of drug-related AEs in the DTG/3TC group (n = 10 [4%]) compared with the EVG/TAF-based regimen group (n = 3 [1%]). The most common drug-related AEs leading to study withdrawal in the DTG/3TC group were psychiatric disorders (n = 7 [3%]).

Over 3 years, participants who switched to DTG/3TC or continued their EVG/TAF-based regimen experienced a small and similar increase in weight (adjusted mean change: DTG/3TC, 2.13 [standard error {SE}, 0.44] kg; EVG/TAF, 1.54 [SE, 0.40] kg), with no significant difference between groups (adjusted treatment difference, 0.59 kg [95% CI, −.57 to 1.76]), consistent with the overall TANGO population (DTG/3TC, 2.22 [SE, 0.35] kg; TAF, 1.73 [SE, 0.33] kg; difference of 0.49 kg [95% CI,



	Total cholesterol, mmol/L		HDL cholesterol, mmol/L		LDL cholesterol, mmol/L		Triglycerides, mmol/L		Total cholesterol/ HDL cholesterol ratio	
Baseline, n	197	202	197	202	197	202	197	202	197	202
Mean (SD)	5.09 (0.95)	5.06 (0.99)	1.41 (0.42)	1.37 (0.36)	2.97 (0.82)	3.01 (0.89)	1.66 (1.28)	1.54 (0.96)	3.85 (1.15)	3.95 (1.28)
Week 48, n	166	167	166	167	166	167	166	167	166	167
Mean (SD)	4.82 (0.94)	5.29 (0.99)	1.34 (0.40)	1.42 (0.39)	2.83 (0.83)	3.17 (0.91)	1.50 (1.34)	1.55 (0.88)	3.85 (1.29)	3.95 (1.17)

Figure 1. Change from baseline to week 144 in fasting lipid parameters for the dolutegravir/lamivudine (DTG/3TC) and elvitegravir (EVG)/tenofovir alafenamide (TAF)–based regimen groups. Error bars represent the upper and lower bounds of the 95% confidence interval (CI). Estimated adjusted ratio (week 144 to baseline) in each group was calculated using a repeated-measures model applied to change from baseline in $\log_e$-transformed data adjusting for treatment, baseline EVG/cobicistat (c)/TAF/emtricitabine (FTC), $CD4^+$ cell count, age, $\log_e$-transformed baseline value, race, baseline body mass index, treatment-by-visit interaction, baseline value-by-visit interaction, treatment-by-EVG/c/TAF/FTC interaction, EVG/c/TAF/FTC-by-visit interaction, and EVG/c/TAF/FTC-by-treatment-by-visit interaction, with visit as the repeated factor. Treatment ratio (95% CI) of DTG/3TC to EVG/TAF-based regimen shown above bars. Mean (standard deviation) at baseline and week 48 shown under bars. [a]Number of participants with nonmissing fasting lipid data at baseline and week 144. Abbreviations: 3TC, lamivudine; c, cobicistat; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; TAF, tenofovir alafenamide.

−.46 to 1.44]) [4]. At week 144, there were small decreases from baseline in all lipid parameters in the DTG/3TC group and small increases from baseline in the EVG/TAF-based regimen group, except for total cholesterol/high-density lipoprotein cholesterol ratio, which remained stable in the EVG/TAF group (Figure 1). Changes in weight and lipids in the baseline EVG subgroup were similar to those observed in the overall population.

DISCUSSION

Approximately two-thirds of the TANGO population was using EVG at baseline, and accordingly, the high proportion of participants maintaining virologic suppression at week 144 seen in the overall population [4] was also observed in this subgroup. Mean change from baseline in $CD4^+$ cell count was comparable between treatment groups among participants in the baseline EVG subgroup, consistent with overall study results. Drug-related AEs occurred more frequently in participants who switched to DTG/3TC in the baseline EVG subgroup and overall, though this is expected when changing from a stable ART regimen [4]. There was no significant difference in weight gain between groups; proportions of participants reporting weight gain as an AE were low and similar. Changes in fasting lipids generally favored DTG/3TC over the EVG/TAF-based regimen, which was also consistent with observations from the overall DTG/3TC and TAF-based regimen groups. Altogether, results from this post hoc subgroup analysis demonstrate the long-term virologic efficacy of switching to DTG/3TC from an EVG/TAF-based regimen for maintenance of virologic suppression in adults with HIV-1.

With the exception of EVG, ART-naive and ART-experienced individuals who use INSTIs as their third agent generally have better lipid profiles compared with those who use boosted protease inhibitors or nonnucleoside reverse transcriptase inhibitors [9–14]. For EVG-based regimens, the association with dyslipidemia has often been attributed to the comparator regimens frequently including tenofovir disoproxil fumarate [12–14], an antiretroviral agent with a known lipid-lowering effect [15]. However, the improvements in lipids observed in the DTG/3TC group in this analysis, where all baseline regimens included TAF, demonstrate an independent risk of dyslipidemia with EVG [16] or suggest that TAF may adversely affect lipid levels [17]. Notably, EVG is the only INSTI currently administered with a pharmacological boosting agent, and boosting agents may contribute to the dyslipidemia

observed with EVG-based regimens, as an elevated incidence of dyslipidemia has been observed with the boosting agent ritonavir [18]. However, results from a study assessing switch from ritonavir to cobicistat showed that cobicistat had a favorable impact on lipid parameters compared with ritonavir [19]. Regardless of the mechanism driving dyslipidemia with use of an EVG/TAF-based regimen, the results here suggest that the effect on plasma lipid levels can be reversed upon switch to DTG/3TC.

The primary limitation of this analysis was that the majority of participants were White, male, and aged <50 years.

Results from this subgroup analysis of the TANGO study at week 144 in participants who used EVG with their TAF-based regimen at baseline are consistent with previous reports in the overall study population [4, 8] and further demonstrate the durable noninferior efficacy of DTG/3TC compared with continuing 3- or 4-drug TAF-based regimens in virologically suppressed adults with HIV-1.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank the study participants and their families and caregivers; the investigators and site staff who participated in the study; and the ViiV Healthcare, GSK, Pharmaceutical Product Development, and Phastar study team members. Editorial assistance was provided under the direction of the authors by Katie Yoest, PhD, and Jennifer Rossi, MA, ELS, MedThink SciCom, and was funded by ViiV Healthcare.

Author contributions. A. Y. R. O., A. M., B. J., and T. W. contributed to the conception of the study. M. A.-K., J. O., and B. W. contributed to the design of the study. M. A.-K., B. W., and B. J. contributed to the acquisition of data. M. A.-K. and J. O. contributed to the analysis of data. M. A.-K., A. Y. R. O., A. M., B. J., and T. W. contributed to the interpretation of data. M. A.-K. and A. Y. R. O. contributed to drafting the manuscript. A. Y. R. O., A. M., and B. J. contributed to critically revising the manuscript for important intellectual content. All authors approved the manuscript for publication.

Patient consent. All participants provided written informed consent before study initiation.

Data availability. Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Financial support. This work was supported by ViiV Healthcare.

Potential conflicts of interest. All authors are employees of ViiV Healthcare or GSK and may own stock in GSK.

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