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Durable Efficacy of Switching From a 3- or 4-Drug Tenofovir Alafenamide–Based Regimen to the 2-Drug Regimen Dolutegravir/Lamivudine in the TANGO Study Through Week 196

Stéphane De Wit, MD[1]; Fabrice Bonnet, MD, PhD[2]; Olayemi Osiyemi, MD[3]; Fiona Bisshop, MBBS[4]; Julian Olalla, MD[5]; Jean-Pierre Routy, MD[6]; Christoph Wyen, MD[7]; Riya Moodley, MD[8]; Keith Pappa, PharmD[9]; Ruolan Wang, MSc[9]; James Oyee, BSc[10]; Parminder Saggu, PhD[10]; Emilio Letang, MD, MPH, PhD[11]; Brian Wynne, MD[9]; Bryn Jones, MBChB, MRCP[8]; Kimberly Y. Smith, MD[9]; Mounir Ait-Khaled, PhD[8]

[1]CHU Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium

[2]CHU de Bordeaux, Service de Médecine Interne et Maladies Infectieuses, and Bordeaux University, INSERM U1219, Bordeaux Population Health, Bordeaux, France

[3]Triple O Research Institute PA, West Palm Beach, FL, USA

[4]Holdsworth House Medical Brisbane, Queensland, Australia

[5]Unidad de Medicina Interna, Hospital Costa del Sol, Marbella, Spain

[6]McGill University Health Centre, Montréal, QC, Canada

[7]Praxis am Ebertplatz, Cologne, Germany

[8]ViiV Healthcare, Brentford, UK

[9]ViiV Healthcare, Durham, NC, USA

[10]GSK, Brentford, UK

[11]ViiV Healthcare, Madrid, Spain

Correspondence and reprint requests to: Mounir Ait-Khaled, PhD, 980 Great West Road, Brentford, Middlesex, UK, TW8 9GS, Phone: +44 208 990 4257, Email: mounir.c.ait-khaled@viivhealthcare.com

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ABSTRACT

Background: Switching to the 2-drug regimen dolutegravir/lamivudine demonstrated durable non-inferior efficacy vs continuing 3- or 4-drug tenofovir alafenamide–based regimens for maintaining virologic suppression in people with HIV-1 through Week 144 in TANGO.

Setting: 134 centers, 10 countries.

Methods: Adults with HIV-1 RNA <50 copies/mL for >6 months and no history of virologic failure were randomized to switch from stable tenofovir alafenamide–based regimens to dolutegravir/lamivudine on Day 1 (early-switch group) for 196 weeks. Those randomized to continue tenofovir alafenamide–based regimens on Day 1 who maintained virologic suppression at Week 144 switched to dolutegravir/lamivudine at Week 148 (late-switch group). Efficacy,

safety, and tolerability (including weight and biomarker changes) of dolutegravir/lamivudine in early-switch and late-switch groups were assessed through Week 196.

Results: Overall, 369 participants switched to dolutegravir/lamivudine on Day 1 (early-switch) and 298 switched at Week 148 (late-switch). In the early-switch group, 83% (306/369) maintained virologic suppression through Year 4, and 3% (11/369) reported new adverse events between Weeks 144 and 196. The late-switch group at Week 196 and early-switch group at Week 48 had comparable proportions with virologic suppression (93% each) and similar safety profiles. No late-switch participants and 1 early-switch participant met confirmed virologic withdrawal criteria through Week 196, with no resistance-associated mutations observed. Treatment continued to be well tolerated long-term.

Conclusion: Switching from tenofovir alafenamide–based regimens to dolutegravir/lamivudine showed durable efficacy, high barrier to resistance, and good tolerability through 4 years. These results support dolutegravir/lamivudine as a robust treatment for maintaining virologic suppression.

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INTRODUCTION

Dolutegravir/Lamivudine is a 2-drug antiretroviral therapy (ART) regimen recommended internationally as a suppressed-switch option in adults with HIV-1 and no history of virologic failure or drug resistance to reduce the number of drugs in a regimen.[1-3] The phase 3 TANGO[4]

trial randomized virologically suppressed adults to switch to once-daily dolutegravir/lamivudine or maintain stable tenofovir alafenamide–based regimens and, as the primary endpoint, assessed proportion of the intention-to-treat–exposed (ITT-E) population with HIV-1 RNA ≥50 copies/mL (Snapshot algorithm) at Week 48. Switching to dolutegravir/lamivudine demonstrated durable and non-inferior efficacy vs continuing tenofovir alafenamide–based regimens for maintaining virologic suppression through 144 weeks, with a high barrier to resistance and well-tolerated safety profile.[5]

In Year 3, TANGO entered a non-randomized phase with all participants receiving dolutegravir/lamivudine. Here, we present 196-week efficacy and safety data for those who switched to dolutegravir/lamivudine on Day 1 and 48-week data for those who switched to dolutegravir/lamivudine at Week 148.

METHODS

Study design

TANGO (ClinicalTrials.gov, NCT03446573) is a randomized, open-label, parallel-group, active-controlled, multi-center, phase 3 study conducted in 10 countries. Study protocols and amendments were reviewed and approved by ethics committees or institutional review boards. TANGO was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before study initiation.

Details for the initial phase of TANGO have been published.[4,5] Briefly, virologically suppressed (HIV-1 RNA <50 copies/mL) adults on an uninterrupted tenofovir alafenamide–

based regimen for >6 months before screening, with no prior virologic failure or documented nucleoside reverse transcriptase inhibitor or integrase strand transfer inhibitor resistance, were eligible.

Procedures

Participants were stratified by baseline third agent class and randomized 1:1 to either switch to once-daily, fixed-dose combination dolutegravir/lamivudine or continue a 3- or 4-drug tenofovir alafenamide–based regimen from Day 1 to Week 148. Participants randomized to receive dolutegravir/lamivudine on Day 1 are referred to as the early-switch (ES) group. Participants randomized to continue tenofovir alafenamide–based regimens from Day 1 to Week 144 switched to dolutegravir/lamivudine at Week 148 and are referred to as the late-switch (LS) group (only those with confirmed virologic suppression at Week 144 were eligible to continue as the LS group).

Plasma HIV-1 RNA viral load testing was performed by Q^2 Solutions Laboratories (Durham, NC) using Abbott HIV-1 Realtime assay (Abbott Molecular, Des Plaines, IL; quantitative detection range, 40-10,000,000 copies/mL). Whole-blood proviral DNA genotyping and plasma HIV-1 RNA genotyping and phenotyping were performed by Monogram Biosciences (South San Francisco, CA) using Genosure® Archive, PhenoSense® IN, PhenoSense® GT, and GeneSeq® IN assays.

Outcomes

Protocol-defined Week 196 exploratory endpoints included proportion of participants with HIV-1 RNA <50 copies/mL (Snapshot; ITT-E) and dolutegravir/lamivudine safety and tolerability. Incidence of confirmed virologic withdrawal (CVW; HIV-1 RNA ≥50 copies/mL followed by a second consecutive HIV-1 RNA ≥200 copies/mL) and viral resistance was

evaluated. Change from baseline in lymphocyte counts; weight; and renal, bone, and inflammatory biomarkers was assessed. For the ES group, baseline refers to Day 1; for the LS group, LS baseline generally refers to Week 148, but if Week 148 data were unavailable, the most recent pre-switch data were used.

Analyses

The ITT-E population included all randomized participants who received ≥1 dose of study treatment. The safety population included ITT-E participants who received the correct assigned treatment. For this non-randomized phase of the study, efficacy was analyzed by Snapshot and observed analyses. Descriptive summary statistics are presented for safety and metabolic health parameters. Data tabulations and calculations were performed using SAS® software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Participants

Overall, 99% (369/371) of randomized participants received dolutegravir/lamivudine from Day 1 through Week 196 (ES group). Of participants randomized to continue tenofovir alafenamide–based regimens on Day 1, 80% (298/372) remained on study, maintained virologic suppression at Week 144, and switched to dolutegravir/lamivudine at Week 148 (LS group). Between Weeks 144 and 196, 12 (3%) ES participants and 24 (8%) LS participants discontinued, most commonly for adverse events (AEs; ES, <1% (2/369); LS, 3% [9/298]) and lost to follow-up (ES, 1% [5/369]; LS, 2% [6/298]; Supplemental Digital Content [SDC] 1, table showing disposition). Demographics and baseline characteristics were generally comparable between

groups (SDC 2, table showing participant characteristics). A higher proportion of participants were aged ≥50 years in the LS group (34%) vs the ES group (21%) at time of dolutegravir/lamivudine start.

Efficacy

At Week 196, high proportions of participants had HIV-1 RNA <50 copies/mL (Snapshot; ITT-E): 83% (306/369) in the ES group after 196 weeks of dolutegravir/lamivudine and 93% (278/298) in the LS group after 48 weeks of dolutegravir/lamivudine (Figure 1). Overall ES and LS group virologic response rates were consistent with rates across various demographic and baseline characteristic subgroups (SDC 3, figure showing virologic response by subgroup). By observed analysis, 99% (306/309) of ES participants on study through Week 196 were virologically suppressed. By Snapshot analysis, no LS participants had HIV-1 RNA ≥50 copies/mL at Week 196. High proportions of both groups also had HIV-1 RNA <40 copies/mL and target not detected, a more stringent measure of virologic suppression (SDC 4, table showing HIV-1 RNA <40 copies/mL).

In the ES group, median (IQR) CD4+ cell count increased from baseline by 22.5 (−71.0, 121.5) cells/mm^3 48 weeks post-switch to dolutegravir/lamivudine and by 65.5 (−47.0, 177.0) cells/mm^3 196 weeks post-switch. In the LS group, CD4+ cell count increased from LS baseline by 53.5 (−35.3, 163.5) cells/mm^3 48 weeks post-switch to dolutegravir/lamivudine. The ES group median (IQR) change from baseline in CD4+/CD8+ ratio was 0.03 (−0.05, 0.11) 48 weeks post-switch to dolutegravir/lamivudine and 0.10 (−0.03, 0.26) 196 weeks post-switch to dolutegravir/lamivudine. The LS group change from LS baseline in CD4+/CD8+ ratio was 0.03 (−0.08, 0.16) 48 weeks post-switch to dolutegravir/lamivudine.

One participant in the ES group met CVW criteria at Week 196; no resistance-associated mutations were observed. Viral load measurements at all post-baseline visits before Week 196 were <50 copies/mL for this participant (except for an unconfirmed 52 copies/mL at Week 172). Although lack of adherence for the Week 196 rebound cannot be excluded, no formal explanation (eg, treatment interruption, intercurrent illness, vaccination, drug-drug interaction) was documented by the investigator. The participant switched to locally available dolutegravir/lamivudine post-CVW, but no post-study HIV-1 RNA data are available.

Safety

Few new AEs were reported between Weeks 144 and 196 in the ES group (Table 1). Safety profiles 48 weeks post-switch to dolutegravir/lamivudine were comparable between the ES (Day 1-Week 48)[4] and LS groups (Weeks 148-196; Table 1). Only 2 serious AEs (SAEs) were considered treatment-related, hypertransaminasemia (n=1, ES group) and type 1 hypersensitivity (n=1, LS group). Few AEs led to withdrawal across 4 years. Of the AEs leading to withdrawal between Weeks 144 and 196, none in the ES group and 9 (n=6 participants) in the LS group were drug-related. None of the 4 fatal AEs were considered treatment-related.

Mean (SD) weight change was 2.70 (6.14) kg after 4 years of dolutegravir/lamivudine in the ES group (0.29-kg increase between Weeks 144 and 196) and 0.43 (4.32) kg after 48 weeks of dolutegravir/lamivudine in the LS group. Proportions of participants with weight increase from baseline above ≥5% or ≥10% thresholds were maintained in the ES group between Weeks 144 and 196 and comparable between the ES and LS groups 48 weeks post-switch to dolutegravir/lamivudine (SDC 5, figure showing weight change by clinically relevant thresholds).

Lipid profiles remained neutral at Week 196, with overall decreases from baseline (ES group) and LS baseline (LS group) in most parameters (SDC 6, figure showing lipid changes). Similar proportions of participants in each group used lipid-modifying agents, both at baseline/LS baseline (ES, 49/369 [13%]; LS, 60/298 [20%]) and 48 weeks post-switch to dolutegravir/lamivudine (ES, 24/369 [7%]; LS, 13/298 [4%]).

Creatinine-adjusted estimated glomerular filtration rate (eGFR) decreased in both groups, with larger decreases in the ES group at all time points (SDC 7A, figure showing renal biomarker changes); at Week 196, cystatin-C–adjusted eGFR decreased vs baseline in the ES group and increased vs LS baseline in the LS group. Minimal changes from baseline/LS baseline were observed in urine renal biomarkers (SDC 7B) and bone biomarkers (SDC 8, figure showing bone biomarker changes). Inflammatory biomarker levels increased or decreased vs baseline levels depending on biomarker, with no consistent trends (SDC 9, figure showing inflammatory biomarker changes).

DISCUSSION

In TANGO, switching from 3- or 4-drug tenofovir alafenamide–based regimens to the 2-drug regimen dolutegravir/lamivudine continued to demonstrate durable high efficacy, a high barrier to resistance, and good tolerability through 4 years in virologically suppressed adults. Consistent with 144-week analyses,[5] high proportions of participants maintained HIV-1 RNA <50 copies/mL (Snapshot; ITT-E) in the ES group at Year 4 (83%), including when the more stringent HIV-1 RNA <40 copies/mL and target not detected endpoint was used (75%). Notably,

by observed analysis, 99% (306/309) of ES participants on study at Week 196 remained virologically suppressed.

At 48 weeks post-switch to dolutegravir/lamivudine, median increases in CD4+/CD8+ ratio vs baseline were consistent between the TANGO dolutegravir/lamivudine ES group (0.03 vs tenofovir alafenamide–based regimen, 0.05)[4] and LS group (0.03). At Week 144, median change from baseline in CD4+/CD8+ ratio was similar between the dolutegravir/lamivudine (0.06) and tenofovir alafenamide–based regimen groups (0.10).[5] The sustained increases observed in the ES and LS groups at Week 196 indicate that dolutegravir/lamivudine maintains positive immunological effects through Year 4.

One CVW was reported in the ES dolutegravir/lamivudine group through Week 196, consistent with the high barrier to resistance observed in other clinical trials.[6-8] The high effectiveness of dolutegravir/lamivudine is also reproduced in real-world settings.[9] A 2021 meta-analysis of 1823 individuals receiving dolutegravir plus lamivudine in real-world studies estimated low virologic failure rates through 48 (1.0%; 95% CI, 0.3-2.0) and 96 weeks (1.0%; 95% CI, 0.2-2.2), which included individuals with drug-resistant mutations or previous virologic failure who would have been ineligible for TANGO participation.[10]

Safety data through 4 years of dolutegravir/lamivudine were consistent with 48-week[4] and 144-week[5] analyses and the safety profiles of the individual components.[11,12] Over 48 weeks post-switch to dolutegravir/lamivudine, a smaller proportion of ES vs LS participants reported drug-related AEs and a greater proportion of ES vs LS participants reported SAEs, but differences were small. Very few additional safety events were reported in the ES group between Years 3 and 4. Weight changes were similar between the dolutegravir/lamivudine and tenofovir alafenamide–based regimen groups throughout the randomized phase, including similar

proportions with ≥10% weight increase at Week 144.[4,5] Proportions of participants with weight gain at or above 5% and 10% thresholds increased from Weeks 48 to 144 and remained stable between Weeks 144 and 196, indicating that clinically meaningful weight change may plateau with long-term dolutegravir/lamivudine use. Lipid profiles remained stable over 4 years in the ES group and were reproduced after 1 year in the LS group, in agreement with the neutral or positive lipid profile changes observed with dolutegravir plus lamivudine use in real-world studies.[13] The clinical impact of such neutral-to-small changes in markers of cardiometabolic health remains to be established. As observed through Week 144,[5] dolutegravir/lamivudine had minimal impact on renal and bone biomarkers, consistent with the known safety profile. The small and inconsistent changes in inflammatory biomarkers continue to demonstrate the neutral impact of dolutegravir/lamivudine on inflammation, consistent with the observed durable virologic suppression.

One limitation is that most TANGO participants were White (80%) and male (93%); however, demographic subgroup outcomes were generally consistent. Whereas the ES group 48-week results were randomized, controlled, and powered to observe statistical differences between the dolutegravir/lamivudine and tenofovir alafenamide groups,[4] the LS group 48-week results were non-comparative. When TANGO began, baseline characteristics were balanced between participants switching to dolutegravir/lamivudine and continuing tenofovir alafenamide–based regimens on Day 1[4]; however, because LS baseline (Week 148) was 3 years after ES baseline (Day 1) per study design, a greater proportion of LS vs ES participants were aged ≥50 years when initiating dolutegravir/lamivudine (34% vs 21%). The LS group also had slightly higher weight, body mass index, and CD4+ cell count compared with the ES group at dolutegravir/lamivudine initiation. Despite these differences, consistency between results from

the ES group at Week 48 and the LS group at Week 196 demonstrate that efficacy and safety outcomes of switching from a tenofovir alafenamide–based regimen to dolutegravir/lamivudine can be reproducible.

These results support dolutegravir/lamivudine as a robust, durable, and non-inferior treatment compared with 3- or 4-drug tenofovir alafenamide–based regimens at Week 144 and demonstrate long-term virologic suppression, a consistent tolerability profile, and high barrier to resistance through Year 4.

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DATA AVAILABILITY STATEMENT

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

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FIGURE LEGEND

Figure 1. Virologic outcomes at Week 196 by **(A)** duration of DTG/3TC exposure and **(B)** Snapshot analysis (ITT-E population). DTG, dolutegravir; ES, early-switch; ITT-E, intention-to-treat exposed; LS, late-switch; 3TC, lamivudine.

Table 1. Summary of AEs in the Early-Switch and Late-Switch Dolutegravir/Lamivudine Groups Through Week 196 (Safety Populations)

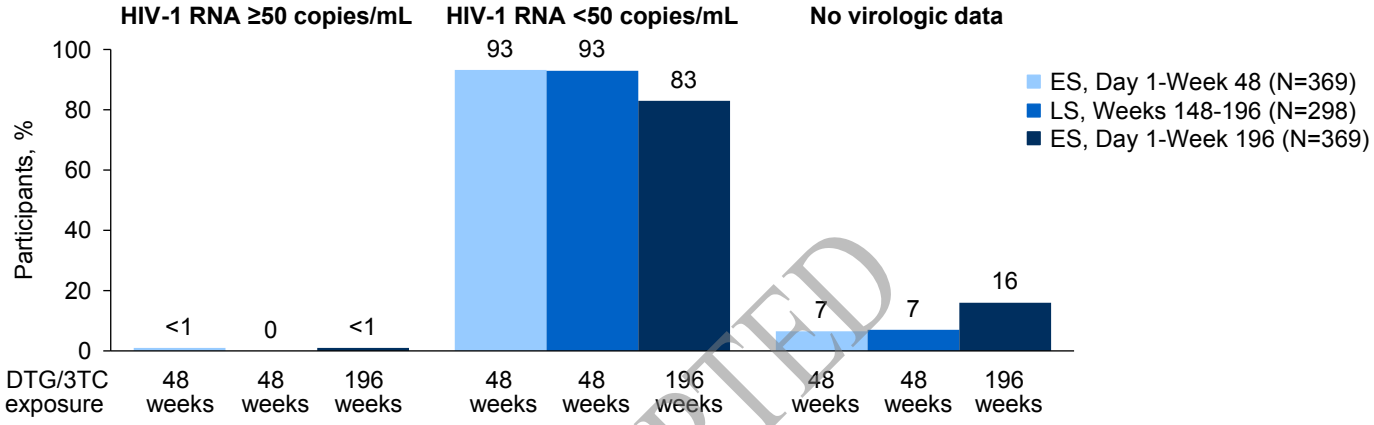
AEs, n (%)	Early-switch dolutegravir/lamivudine (N=369)			Late-switch dolutegravir/lamivudine (N=298)
	Day 1-Week 48	Day 1-Week 144	Day 1-Week 196	Weeks 148-196
Any AE	295 (80)	336 (91)	347 (94)	239 (80)
AEs in ≥10% of participants[a]				
COVID-19	—	33 (9)	77 (21)	55 (18)
Nasopharyngitis	43 (12)	63 (17)	71 (19)	16 (5)
Diarrhea	30 (8)	50 (14)	54 (15)	12 (4)
Upper respiratory tract infection	31 (8)	50 (14)	52 (14)	7 (2)
Syphilis	24 (7)	39 (11)	49 (13)	14 (5)
Back pain	21 (6)	43 (12)	47 (13)	11 (4)
Arthralgia	12 (3)	31 (8)	46 (12)	15 (5)
Anxiety	17 (5)	35 (9)	44 (12)	7 (2)
Headache	24 (7)	35 (9)	41 (11)	17 (6)
AEs leading to withdrawal	13 (4)	23 (6)	25 (7)	9 (3)
Grade 2-5 AEs	193 (52)	279 (76)	295 (80)	165 (55)
Drug-related grade 2-5 AEs	17 (5)	21 (6)	23 (6)	11 (4)

Serious AEs	21 (6)	57 (15)	65 (18)	15 (5)
Fatal AEs[b]	1 (<1)	3 (<1)	4 (1)	0

AE, adverse event.

[a]Based on AEs reported in ≥10% of early-switch participants from Day 1-Week 196. [b]Fatal AEs were gunshot wound (homicide; Day 1-Week 48), substance abuse (Weeks 48-144), ischemic hepatitis (Weeks 48-144), and acute myocardial infarction (Weeks 144-196); none were considered related to study treatment.

A



B

Outcome, n (%)	ES DTG/3TC (N=369) Day 1-Week 48	ES DTG/3TC (N=369) Day 1-Week 196	LS DTG/3TC (N=298) Weeks 148-196
HIV-1 RNA <50 copies/mL	344 (93)	306 (83)	278 (93)
HIV-1 RNA ≥50 copies/mL	1 (<1)	3 (<1)	0
Data in window and not below threshold	0	2 (<1)	0
Non–COVID-19 related	1 (<1)	1 (<1)	0
Discontinued for lack of efficacy	0	0	0
Discontinued for other reason and not below threshold	1 (<1)	1 (<1)	0
No virologic data	24 (7)	60 (16)	20 (7)
Non–COVID-19 related	24 (7)	58 (16)	20 (7)
Discontinued due to adverse event or death	12 (3)	24 (7)	8 (3)
Discontinued for other reason	12 (3)	32 (9)	11 (4)
On study but missing data in window	0	2 (<1)	1 (<1)
COVID-19 related	—	2 (<1)	0
Discontinued for other reason	—	2 (<1)	0