SWITCHING TO DTG/3TC FIXED-DOSE COMBINATION (FDC) IS NON-INFERIOR TO CONTINUING A TAF-BASED REGIMEN IN MAINTAINING VIROLOGIC SUPPRESSION THROUGH 144 WEEKS (TANGO STUDY)

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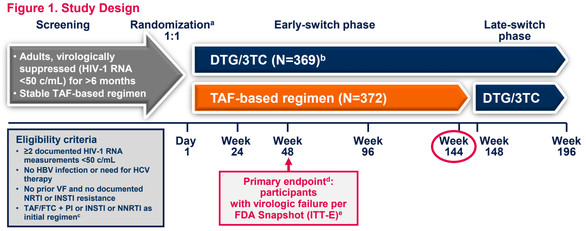
Introduction

- 2-drug regimens (2DRs) have been investigated as a means for reducing the number of antiretroviral agents taken by individuals who need lifelong ART[1]
- In treatment-naive individuals, the 2DR DTG + 3TC was non-inferior to DTG + TDF/FTC in the primary analysis of the GEMINI-1 and -2 studies at Week 48 and longer-term analyses at Weeks 96 and 144[2-4]
- In treatment-experienced individuals, DTG/3TC was non-inferior to continuing any current ART regimen in treatment-experienced adults with HIV-1 at Week 48 in the SALSA study[5]
- Additionally, in the TANGO study, switching to DTG/3TC FDC was non-inferior to remaining on a TAF-based regimen in virologically suppressed adults at Weeks 48, 96, and 144[6-8]
  - Here we present further secondary endpoint analyses from TANGO at Week 144

Methods

- TANGO is an ongoing, phase III, non-inferiority trial evaluating efficacy and safety of switching to DTG/3TC FDC in adults with HIV-1 who are virologically suppressed on a 3- or 4-drug TAF-based regimen (Figure 1)

Figure 1. Study Design



[a]Stratified by baseline third agent class (PI, INSTI, or NNRTI). [b]2 participants excluded who were randomized but not exposed to study drug. [c]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [d]4% non-inferiority margin. [e]Includes participants who changed a background therapy component or discontinued study treatment for lack of efficacy before Week 48, or who had HIV-1 RNA ≥50 c/mL in the 48-week window.

- The primary endpoint was proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot algorithm in the ITT-E population)
- Secondary and exploratory analyses included Week 144 efficacy (Snapshot); safety (incidence and severity of AEs); and change from baseline in weight, lipids, renal biomarkers, and inflammatory biomarkers

Results

Participants

- In the ITT-E population, 741 participants were randomized to switch to DTG/3TC (n=369) or continue their TAF-based regimen (n=372)
- Demographics and baseline characteristics were similar between treatment groups (Table 1)

Table 1. Demographics and Baseline Characteristics

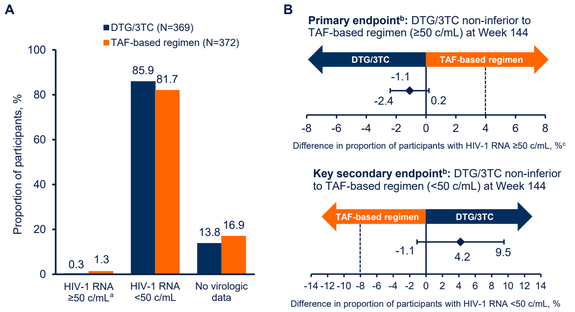
Characteristic, n (%)[a]	DTG/3TC (N=369)	TAF-based regimen (N=372)
Age, median (range), y	40 (20-74)	39 (18-73)
≥50 y	79 (21)	92 (25)
Female	25 (7)	33 (9)
Race		
African American/African heritage	50 (14)	58 (16)
Asian	13 (4)	13 (3)
White	297 (80)	289 (78)
Other	9 (2)	12 (3)
Weight, median (range), kg	78.5 (50.2-153.0)	79.8 (47.6-141.0)[b]
BMI, median (range), kg/m^2	25.2 (17.4-47.1)	25.7 (15.7-54.0)[b]
CD4+ cell count, median (range), cells/mm^3	682 (133-1904)	720 (119-1810)
Baseline third agent class		
INSTI	289 (78)	296 (80)
EVG/c	243 (66)	249 (67)
NNRTI	51 (14)	48 (13)
RPV	43 (12)	45 (12)
PI	29 (8)	28 (8)
bDRV	25 (7)	27 (7)
Historical genotypic resistance test results available at screening, n (%)[c]	221 (60)	243 (65)
Duration of ART before Day 1, median (range), mo	33.8 (7.1-201.2)	35.1 (7.0-160.8)
Duration of TAF before Day 1, median (range), mo	17.7 (3.6-73.7)	18.2 (3.9-71.2)

[a]Unless otherwise indicated. [b]N=371. [c]Historical resistance test results provided at screening were not recorded in the electronic case report form nor were they part of the locked database but are data on file that have been source verified and archived in the study trial master file.

Virologic and Immunologic Outcomes

- At Week 144, 0.3% (1/369) of participants in the DTG/3TC group and 1.3% (5/372) in the TAF-based regimen group had HIV-1 RNA ≥50 c/mL (Snapshot, ITT-E), demonstrating continued non-inferiority of DTG/3TC (adjusted treatment difference, −1.1%; 95% CI, −2.4% to 0.2%; Figure 2)

Figure 2. Efficacy Results (Snapshot)



[a]Primary endpoint (Snapshot virologic non-response, ITT-E). [b]Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC − TAF-based regimen) adjusting for baseline third agent class. [c]For per-protocol analysis: adjusted difference, −1.1%; 95% CI, −2.3% to −0.030851%).

- In the per-protocol population (sensitivity analysis), superiority of DTG/3TC was demonstrated with 0/345 participants in the DTG/3TC group and 4/349 (1%) in the TAF-based regimen group with HIV-1 RNA ≥50 c/mL at Week 144 (adjusted difference, −1.1%; 95% CI, −2.3% to −0.0%; *P*=0.044)
- Results from the efficacy data evaluable population were consistent with the main ITT-E analyses (Table 2)

Table 2. Snapshot Outcomes at Week 144

	ITT-E		Efficacy data evaluable[a]	
n (%)	DTG/3TC (N=369)	TAF-based regimen (N=372)	DTG/3TC (N=364)	TAF-based regimen (N=370)
HIV-1 RNA <50 c/mL	317 (86)	304 (82)	317 (87)	304 (82)
HIV-1 RNA ≥50 c/mL	1 (<1)	5 (1)	1 (<1)	5 (1)
Data in window and HIV-1 RNA ≥50 c/mL	0	0	0	0
Discontinued for lack of efficacy	0	4 (1)	0	4 (1)
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	1 (<1)	0	1 (<1)	0
Change in ART	0	1 (<1)	0	1 (<1)
No virologic data	51 (14)	63 (17)	46 (13)	61 (16)
Non–COVID-19 related	46 (12)	61 (16)	46 (13)	61 (16)
Discontinued because of AE or death[b]	23 (6)	6 (2)	23 (6)	6 (2)
Discontinued for other reasons[c]	22 (6)	55 (15)	22 (6)	55 (15)
Missing data during window but on study	1 (<1)	0	1 (<1)	0
COVID-19 related	5 (1)	2 (<1)	NA	NA
Discontinued because of AE or death	0	0	NA	NA
Discontinued for other reasons[c]	2 (<1)	2 (<1)	NA	NA
Missing data during window but on study	3 (<1)	0	NA	NA

[a]Sensitivity analysis excluding 5 and 2 participants in the DTG/3TC and TAF-based regimen groups, respectively, because of no Week 144 HIV-1 RNA data due to effects of the COVID-19 pandemic. [b]3 fatal AEs unrelated to study treatment occurred (homicide, acute intoxication, and ischemic hepatitis in the DTG/3TC group) by Week 144. [c]Other reasons for discontinuation through Week 144 included protocol deviation, lost to follow-up, physician decision, withdrawal by participant, and lack of efficacy (in 2 participants in the TAF-based regimen group).

- Proportion of participants with HIV-1 RNA <40 c/mL and target not detected status at Week 144 was 76% (279/369) in the DTG/3TC group and 72% (267/372) in the TAF-based regimen group (ITT-E population; adjusted treatment difference, 3.9%; 95% CI, −2.5% to 10.2%)
- At Week 144, no participants in the DTG/3TC group and 3 (0.8%) in the TAF-based regimen group met confirmed virologic withdrawal (CVW) criteria, with no resistance observed at failure
- Median (IQR) change from baseline to Week 144 in CD4+ cell count was 36.0 cells/mm^3 (−64.0, 154.0) in the DTG/3TC group and 35.0 cells/mm^3 (−60.0, 134.0) in the TAF-based regimen group
- For 7 participants with archived M184V/I (all detected as mixtures with wild-type) at baseline, 4 of 4 in the DTG/3TC group and 2 of 3 in the TAF-based regimen group had post-baseline viral load <50 c/mL at all time points through last on-study viral load measurement (post hoc, retrospective analysis of proviral DNA genotyping)

Safety

- Overall rate of any AEs was comparable between groups through Week 144 (Table 3)

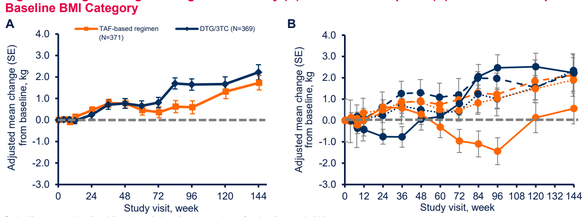
Table 3. AEs Through Week 144

n (%)	DTG/3TC (N=369)	TAF-based regimen (N=371)
Any AE	336 (91)	335 (90)
AEs occurring in ≥12% of participants in either group		
Nasopharyngitis	63 (17)	64 (17)
Upper respiratory tract infection	50 (14)	42 (11)
Diarrhea	50 (14)	44 (12)
Back pain	43 (12)	49 (13)
AEs, Week 48 to Week 144[a]	289 (85)	283 (83)
Drug-related AEs	55 (15)	18 (5)
Drug-related AEs, Week 48 to Week 144[a]	12 (4)	13 (4)
Metabolism and nutrition disorders occurring in ≥1% of participants in either group		
Weight increased	17 (5)	19 (5)
Hyperlipidemia	7 (2)	7 (2)
Weight decreased	3 (<1)	4 (1)
AEs leading to study withdrawal	23 (6)	7 (2)
AEs leading to study withdrawal, Week 48 to 144[a]	9 (3)	5 (1)
Serious AEs[b]	57 (15)	44 (12)
Serious AEs, Week 48 to Week 144[a]	41 (12)	33 (10)

[a]N=342 for both groups. [b]1 drug-related serious AE occurred in each treatment group (DTG/3TC, increased transaminases; TAF-based regimen, angioedema).

- Adjusted mean change in weight from baseline to Week 144 was 2.2 kg in the DTG/3TC group and 1.7 kg in the TAF-based regimen group (Figure 3A); weight loss between Weeks 48 and 96, which was regained at Week 144, occurred in participants in the TAF-based regimen group with obesity at baseline (Figure 3B)

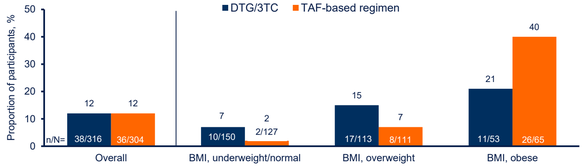
Figure 3. Weight Change Through Week 144 by (A) Treatment Group and (B) Treatment Group and Baseline BMI Category



Dashed line represents baseline. Adjusted mean is the estimated mean change from baseline at each visit in each group calculated using mixed-model repeated measures adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, baseline weight (continuous), prior TAF duration (continuous), region, treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. n refers to number of participants in each subgroup randomized to DTG/3TC or TAF-based regimen from the safety population. Underweight/Normal BMI, ≤24.99 kg/m^2; overweight BMI, 25-29.99 kg/m^2; obese BMI, ≥30 kg/m^2.

- In a post hoc analysis, overall proportion of participants referred for dietetic counseling/weight management programs was similar between treatment groups through Week 144; a higher proportion of participants with baseline BMI classified as obese was referred for weight management intervention in the TAF-based regimen group compared with the DTG/3TC group (Figure 4)

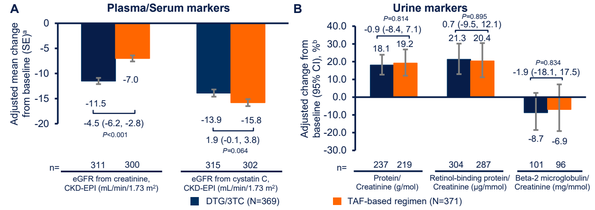
Figure 4. Participants Referred for Diet and Exercise Intervention From Day 1 to Week 144



Weight intervention event was based on source medical notes with affirmative response to "Was this patient advised or referred for dietetic counseling/weight management program including exercise?" n is the number of participants with weight data recorded at the last visit of the reported period and response to survey question available.

- Proportion of participants with ≥10% weight increase from baseline was similar in the DTG/3TC (13%; 42/316) and TAF-based regimen groups (12%; 37/303)
- Lipid changes generally favored DTG/3TC
  - Percent change from baseline based on log$_e$-transformed data at Week 144 in the DTG/3TC vs TAF-based regimen group, respectively: total cholesterol, −3.3% vs 4.2%, *P*<0.001; HDL-C, −2.4% vs 3.9%, *P*<0.001; LDL-C, −3.0% vs 4.6%, *P*<0.001; triglycerides, −9.7% vs 2.2%, *P*=0.001; TC/HDL-C ratio, −0.9% vs 0.3%, *P*=0.501
- Small and similar changes between groups were observed in renal biomarkers at Week 144 (Figure 5)

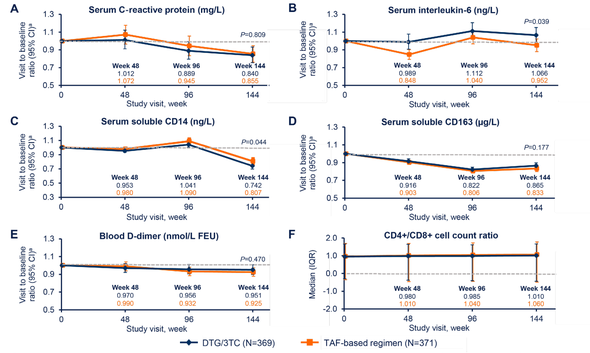
Figure 5. Change From Baseline at Week 144 in (A) Plasma/Serum and (B) Urine Renal Biomarkers



[a]Estimated mean change from baseline at Week 144 in each group calculated from mixed-model repeated measures adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, BMI (continuous), presence of diabetes mellitus, presence of hypertension, baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. [b]Based on estimated geometric mean ratios of Week 144 vs baseline. Based on the same model as plasma/serum biomarkers except adjusting for log$_e$-transformed baseline biomarker. n indicates number of participants with non-missing data at baseline and Week 144.

- Similar and minimal changes from baseline to Week 144 in inflammatory biomarkers were generally observed across treatment groups (Figure 6)
  - Changes in IL-6 favored the TAF-based regimen group; changes in sCD14 favored the DTG/3TC group, although clinical significance is unknown as the changes were minimal
  - Median baseline CD4+/CD8+ ratio was ~1 in both treatment groups and was maintained through Week 144

Figure 6. Inflammatory Biomarkers Through Week 144: Change From Baseline in (A) CRP, (B) IL-6, (C) sCD14, (D) sCD163, and (E) D-dimer. (F) Median CD4+/CD8+ Cell Count Ratio



[a]Ratio is the estimated adjusted ratio (Week 144 to baseline) in each group calculated using mixed-model repeated measures applied to change from baseline in log$_e$-transformed data adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, BMI (continuous), smoking status, HCV co-infection status, log$_e$-transformed baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor.

Conclusions

- At Week 144, switching to DTG/3TC FDC was non-inferior to remaining on a TAF-based regimen in ART-experienced, virologically suppressed adults
- No CVWs were observed in the DTG/3TC group; no resistance was observed in either group
- No new safety signals were observed through Week 144, with similar rates of AEs, drug-related AEs, AEs leading to discontinuation, and serious AEs between treatment groups after Week 48
- Change from baseline in weight was similar between groups; fluctuations observed in participants with baseline obesity may have been impacted by weight management interventions
- Minimal and similar changes in inflammatory and immune activation markers were observed in the 2DR and 3/4DR groups through Week 144
- DTG/3TC offers a robust switch option with high levels of durable efficacy, good safety and tolerability, and a high barrier to resistance through 3 years

Acknowledgments: This study was funded by ViiV Healthcare. The authors would like to acknowledge Nisha George for her contributions to data analysis. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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