METABOLIC HEALTH OUTCOMES AT WEEK 144 IN THE TANGO STUDY, COMPARING A SWITCH TO DTG/3TC VERSUS MAINTENANCE OF TAF-BASED REGIMENS

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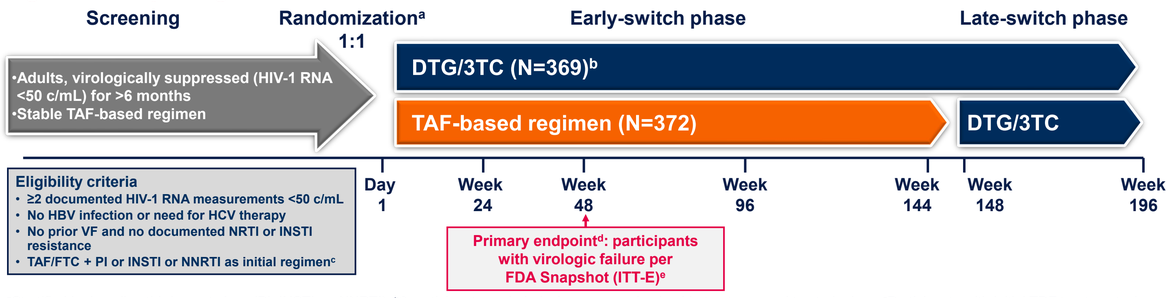
Introduction

- The 2-drug regimen DTG/3TC was non-inferior to TAF-based 3/4-drug regimens in maintaining virologic suppression in adults with HIV-1 infection through Week 96 of the TANGO study[1,2]
- Weight gain and adverse metabolic health outcomes have been associated with certain antiretroviral therapies
  - Increased weight has been associated with the INSTIs DTG, BIC, RAL, and EVG/c[3-5]
  - The NRTI TAF has been associated with increased weight in PLWH[3,4,6] and HIV-negative individuals taking PrEP[7]
  - In the ADVANCE study, participants treated with DTG + TAF/FTC experienced greater weight gain and higher rates of incident obesity and metabolic syndrome compared with those treated with DTG + TDF/FTC and EFV + TDF/FTC[4]
- Here, we present virologic and metabolic health outcomes at Week 144 among participants in the TANGO study

Methods

- TANGO is a phase 3, randomized, open-label, multicenter, non-inferiority study (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 intention-to-treat–exposed [ITT-E] population)
- Secondary analyses were Week 144 efficacy (Snapshot) and clinical safety (incidence and severity of AEs/SAEs)
- The following metabolic health parameters were assessed at Week 144 of TANGO:
  - Change from baseline in weight, fasting lipids, and glucose
  - Prevalence of insulin resistance (HOMA-IR ≥2) and metabolic syndrome
- Mixed models for repeated measures analysis was performed on change from baseline in metabolic health parameters; a logistic regression model was used to determine variables associated with ≥10% weight gain by baseline BMI category, adjusting for relevant baseline variables

Results

Participants

- In the ITT-E population, 741 participants were randomized to the DTG/3TC or TAF-based regimen groups (Table 1)

Table 1. Participant Disposition Through Week 144

Status, n (%)	DTG/3TC (N=369)	TAF-based regimen (N=372)
Ongoing	319 (86)	299 (80)
Withdrawn	50 (14)	73 (20)
AE	23 (6)[a]	7 (2)[b]
Lack of efficacy	0	6 (2)
Protocol deviation	5 (1)	6 (2)
Lost to follow-up	4 (1)	10 (3)
Physician decision	2 (<1)	11 (3)
Withdrawn by participant	16 (4)	33 (9)

[a]Outcome of AEs leading to study withdrawal: 20/369 (5%) were non-fatal and 3/369 (<1%) were fatal. [b]Outcome of AEs leading to study withdrawal: 7/372 (2%) were non-fatal.

- Demographics and baseline characteristics were similar between treatment groups (Table 2)

Table 2. Demographics and Baseline Characteristics

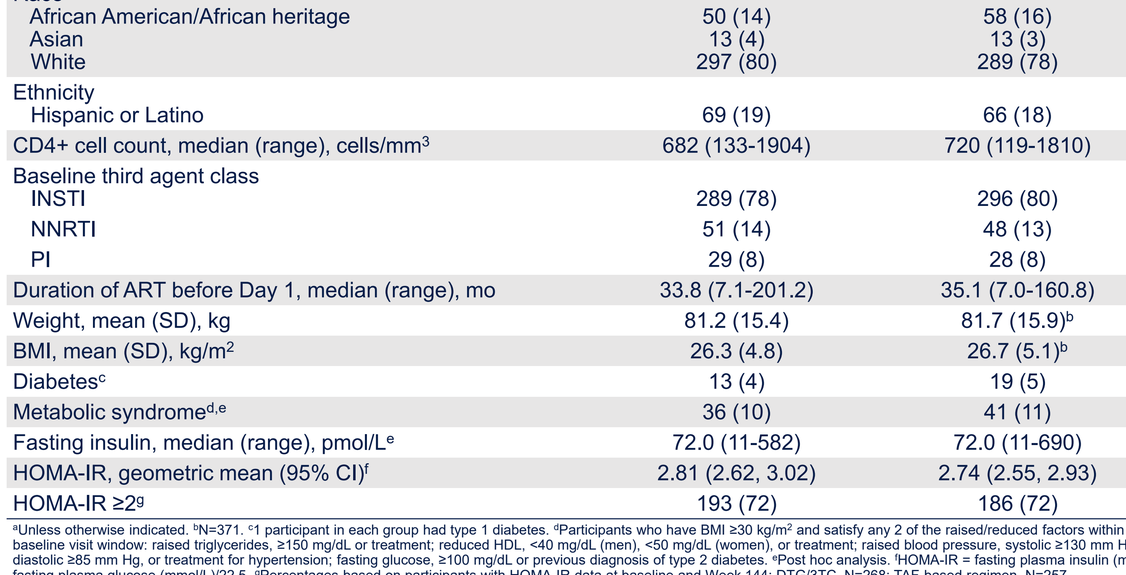
Characteristic, n (%)[a]	DTG/3TC (N=369)	TAF-based regimen (N=372)
Age, median (range), y	40 (20-74)	39 (18-73)
Female	25 (7)	33 (9)
Race		
African American/African heritage	50 (14)	58 (16)
Asian	13 (4)	13 (3)
White	297 (80)	289 (78)
Ethnicity		
Hispanic or Latino	69 (19)	66 (18)
CD4+ cell count, median (range), cells/mm^3	682 (133-1904)	720 (119-1810)
Baseline third agent class		
INSTI	289 (78)	296 (80)
NNRTI	51 (14)	48 (13)
PI	29 (8)	28 (8)
Duration of ART before Day 1, median (range), mo	33.8 (7.1-201.2)	35.1 (7.0-160.8)
Weight, mean (SD), kg	81.2 (15.4)	81.7 (15.9)[b]
BMI, mean (SD), kg/m^2	26.3 (4.8)	26.7 (5.1)[b]
Diabetes[c]	13 (4)	19 (5)
Metabolic syndrome[d,e]	36 (10)	41 (11)
Fasting insulin, median (range), pmol/L[e]	72.0 (11-582)	72.0 (11-690)
HOMA-IR, geometric mean (95% CI)[f]	2.81 (2.62, 3.02)	2.74 (2.55, 2.93)
HOMA-IR ≥2[g]	193 (72)	186 (72)

[a]Unless otherwise indicated. [b]N=371. [c]1 participant in each group had type 1 diabetes. [d]Participants who have BMI ≥30 kg/m^2 and satisfy any 2 of the raised/reduced factors within the baseline visit window: raised triglycerides, ≥150 mg/dL or treatment; reduced HDL, <40 mg/dL (men), <50 mg/dL (women), or treatment; raised blood pressure, systolic ≥130 mm Hg or diastolic ≥85 mm Hg, or treatment for hypertension; fasting glucose, ≥100 mg/dL or previous diagnosis of type 2 diabetes. [e]Post hoc analysis. [f]HOMA-IR = fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5. [g]Percentages based on participants with HOMA-IR data at baseline and Week 144: DTG/3TC, N=268; TAF-based regimen, N=257.

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)
- 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)
- At Week 144, zero participants in the DTG/3TC group and 3 (0.8%) in the TAF-based regimen group met criteria for confirmed virologic withdrawal 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) and 35.0 cells/mm^3 (−60.0, 134.0) in the DTG/3TC and TAF-based regimen groups, respectively

Figure 2. Efficacy Results

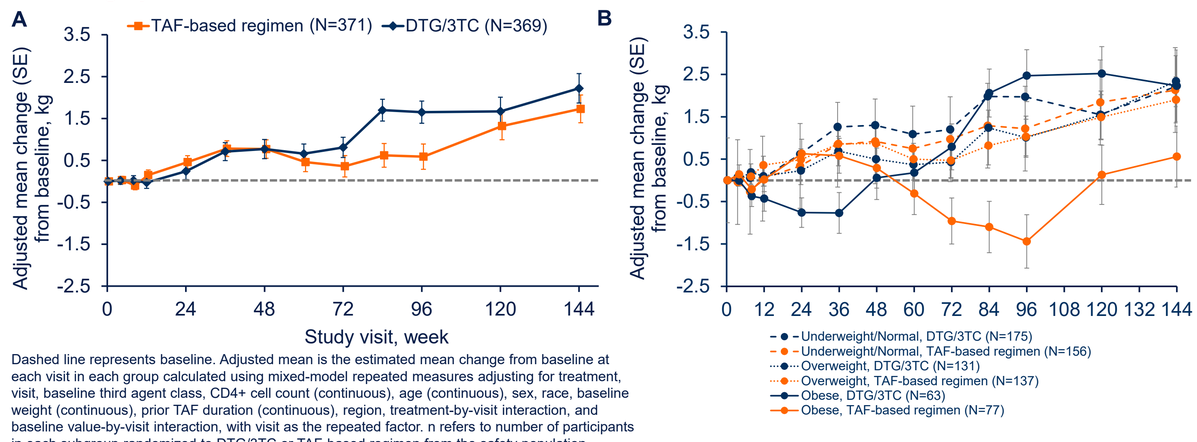


[a]Primary endpoint (Snapshot virologic non-response, ITT-E).
[b]Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC − TAF-based regimen) adjusting for baseline third agent class.

Metabolic Health Outcomes

- Adjusted mean change in weight from baseline to Week 144 was comparable between the DTG/3TC and TAF-based regimen groups (2.2 vs 1.7 kg; Figure 3A; median [IQR] change in weight, 2.2 [−0.8, 5.6] vs 1.3 [−1.5, 5.0] kg, respectively)
- Unexplained 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)
- Weight gain of ≥5% and ≥10% from baseline, respectively, was observed in 39% (123/316) and 13% (42/316) of participants switching to DTG/3TC and 31% (94/303) and 12% (37/303) of participants continuing a TAF-based regimen
- Per logistic regression analysis, the proportion of participants with ≥10% weight gain at Week 144 across baseline BMI categories was comparable between groups; baseline variables associated with weight gain ≥10% were prior TAF duration per year (odds ratio, 0.74; 95% CI, 0.55-0.99), age per 10 years (0.79; 0.62-1.00), and female sex (2.30; 1.01- 5.26)

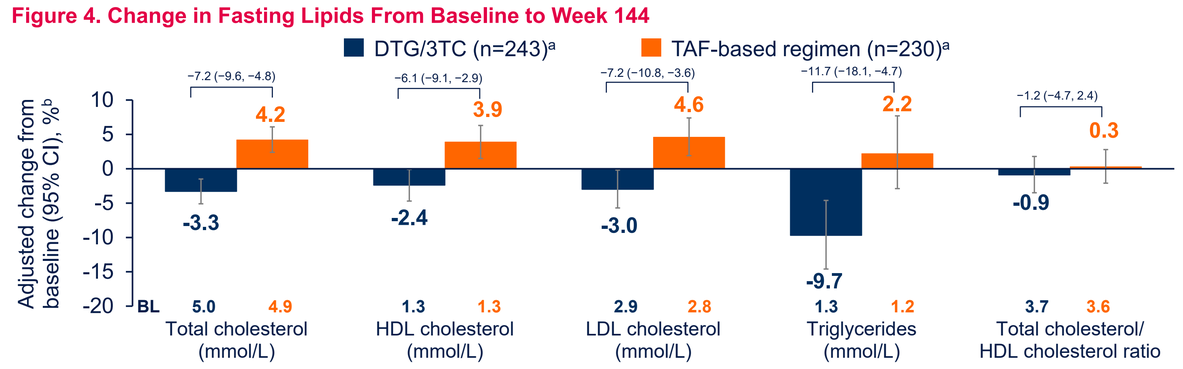
Figure 3. Weight Change Through Week 144 (A) by Treatment Group and (B) by Treatment Group and Baseline BMI Category



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.

- Change in fasting lipids from baseline to Week 144 generally favored DTG/3TC (Figure 4)
  - Post-baseline lipid-modifying agent use occurred in 12% (45/369) of the DTG/3TC group and 11% (42/372) of the TAF-based regimen group

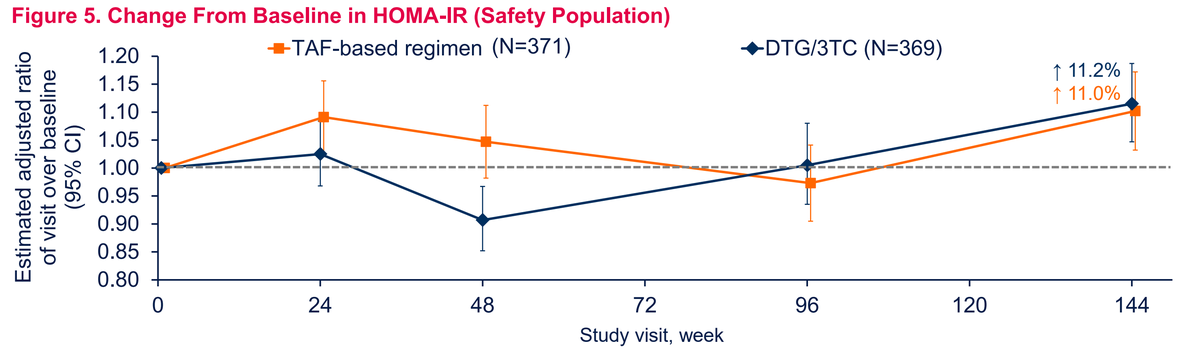
Figure 4. Change in Fasting Lipids From Baseline to Week 144



[a]Number of participants with non-missing fasting lipid data at baseline and Week 144, excluding those with lipid-modifying agent administered at baseline (lipid data collected after initiation of a lipid-modifying agent were censored and LOCF method was applied). Use of lipid-modifying agents at baseline was similar between groups (DTG/3TC, 13%; TAF-based regimen, 15%). [b]Percent change from baseline based on adjusted ratio (Week 144 to baseline) in each group calculated from mixed-model repeated measures applied to change from baseline in $\log_e$-transformed data adjusting for age (continuous), BMI (continuous), treatment, visit, race, baseline third agent class, CD4+ cell count (continuous), $\log_e$-transformed baseline value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. Median baseline (BL) values for each parameter shown below adjusted mean treatment difference (95% CI) value.

- Median (IQR) change from baseline in glucose at Week 144 was 0.0 mmol/L (−0.4, 0.3) in the DTG/3TC group and −0.1 mmol/L (−0.4, 0.3) in the TAF-based regimen group
- Changes in insulin resistance were small and similar between treatment groups at Week 144 (Figure 5)
  - Of participants with baseline and Week 144 HOMA-IR data, 78% of participants in the DTG/3TC group and 82% in the TAF-based regimen group had insulin resistance defined as HOMA-IR ≥2 at Week 144 (odds ratio, 0.78; 95% CI, 0.49-1.24; *P*=0.297)

Figure 5. Change From Baseline in HOMA-IR (Safety Population)



Dashed line represents baseline. Change from baseline was 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), presence of hypertension, $\log_e$-transformed baseline HOMA-IR (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor.

- At Week 144, proportions of participants with metabolic syndrome were 15% and 16% in the DTG/3TC and TAF-based regimen groups, respectively

Safety

- Overall rates of AEs were comparable between groups through Week 144 (Table 3)
- The most frequent AEs (>10% in either group) were nasopharyngitis, diarrhea, back pain, upper respiratory tract infection, syphilis, and arthralgia and were reported in similar proportions across treatment groups

Table 3. Overall Safety and Metabolic Adverse Events Through Week 144

n (%)	DTG/3TC (N=369)	TAF-based regimen (N=371)
Any AE	336 (91)	335 (90)
Drug-related AEs	55 (15)	18 (5)
Drug-related AEs, Week 48 to Week 144[a]	12 (4)	13 (4)
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	57 (15)	44 (12)
Metabolism and nutrition disorders		
Weight increased	17 (5)	19 (5)
Hyperlipidemia	7 (2)	7 (2)
Weight decreased	3 (<1)	4 (1)
Impaired glucose tolerance	1 (<1)	2 (<1)
Type 1 diabetes	1 (<1)	0
Type 2 diabetes	2 (<1)	1 (<1)

[a]N=342 for both groups.

Conclusions

- After 3 years of therapy, DTG/3TC maintained non-inferior efficacy vs TAF-based regimens in treatment-experienced adults, with zero participants with confirmed virologic failure or observed resistance in the DTG/3TC treatment group
- Weight changes were similar between treatment groups and comparable to what would be expected in the general population (0.5-1.0 kg/year)[8]
- Changes in lipids generally favored the DTG/3TC group; changes in other metabolic health parameters were generally similar between groups
- Long-term follow-up and evaluation of the potential effects of ART and diet/exercise on weight and metabolic outcomes for PLWH remain important

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