SWITCHING FROM A 3-DRUG TENOFOVIR ALAFENAMIDE (TAF)-BASED REGIMEN TO A 2-DRUG DOLUTEGRAVIR/LAMIVUDINE (2DR, DTG/3TC FDC) WAS NOT ASSOCIATED WITH A HIGHER FREQUENCY OF INTERMITTENT VIREMIA IN SUPPRESSED PATIENTS IN THE TANGO STUDY

Ruolan Wang,[1] Joe Horton,[2] Jonathan Wright,[3] Rifaz Razeek,[3] Mounir Ait-Khaled,[4] Maria Claudia Nascimento,[4] Allan R. Tenorio,[1] Mark Underwood[1]

[1]ViiV Healthcare, Research Triangle Park, NC, USA; [2]Paraxel International, Durham, NC, USA; [3]GlaxoSmithKline, Stockley Park, UK; [4]ViiV Healthcare, Brentford, UK

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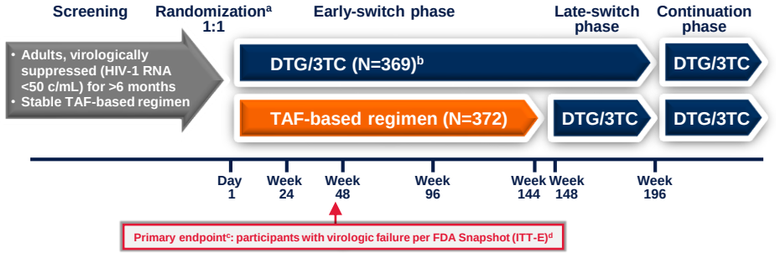
Introduction

- TANGO is a 200-week, phase III, randomized, open-label trial to evaluate efficacy and safety of switching from a TAF-based regimen to a 2DR of DTG/3TC in HIV-1–infected adults with HIV-1 RNA <50 c/mL and without prior virologic failure or historical NRTI or INSTI major resistance mutations at study entry (Figure 1)[1]
- Switching to DTG/3TC was non-inferior to continuing a TAF-based regimen through Week 48 using a 4% non-inferiority margin for Snapshot virologic failure (HIV-1 RNA ≥50 c/mL)[1]
- We assessed elevated viral loads (VLs) through 48 weeks of therapy overall, by study visit and in a subset of participants with archived resistance mutations

Figure 1. TANGO 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]4% non-inferiority margin. [d]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.

Methods

- Elevated viral loads (EVLs, HIV-1 RNA ≥50 c/mL) for exposed participants (intention-to-treat–exposed [ITT-E population]) with at least one post-baseline, on-treatment plasma HIV-1 RNA were assessed in 2 major categories (Table 1): (1) with only VL ≥50 to <200 c/mL, or (2) at least one VL ≥200 c/mL
  - Each of these major categories was further divided into a single non-consecutive occurrence or >2 consecutive occurrence sub-categories
  - A **"blip"** is defined here as a VL of 50 to <200 c/mL with adjacent values <50 c/mL
- Confirmed virologic withdrawal (CVW) criteria were defined as 2 consecutive on-treatment VL ≥50 c/mL with the second VL ≥200 c/mL
- Proviral DNA genotyping was conducted retrospectively on baseline whole blood samples using GenoSure Archive assay by Monogram Biosciences

Results

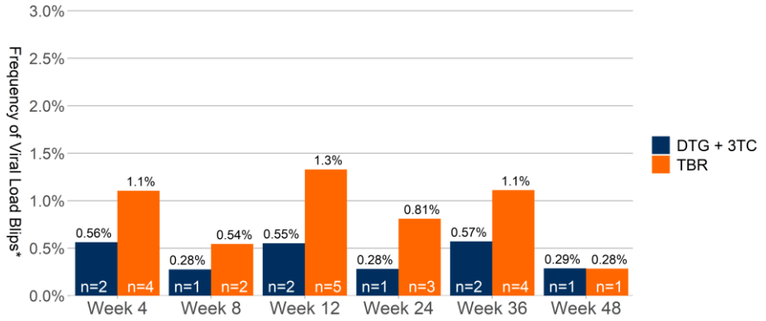
- The proportion of participants with EVLs through 48 weeks of treatment (Table 1) was low and comparable across groups; most frequently observed VL rebounds were in Category 1a
  - The proportion of Category 1a participants with blips by study visit is shown in Figure 2
- By Week 48, no participant in the DTG/3TC group met CVW criteria
- One participant on TAF-based regimen without any pre-existing resistance met CVW criteria
  - No blips occurred before CVW and no emergent resistance was observed at failure

Table 1. Summary of Participants With Elevated Viral Load Categories Through Week 48

Elevated VL categories for participants in the ITT-E population	DTG/3TC FDC (N=369) n (%)	TAF-based regimen (N=372) n (%)
1. Participants with VLs between 50 to <200 c/mL and no VL ≥200 c/mL	**11 (3%)**	**22 (6%)**
1a. VLs between 50 to <200 c/mL with adjacent values <50 c/mL (**"blips"**)	9 (2%)	18 (5%)
1b. ≥2 consecutive VLs between 50 to <200 c/mL	2 (<1%)	4 (1%)
2. Participants with at least one VL ≥200 c/mL	**3 (<1%)**	**3 (<1%)**
2a. A single VL ≥200 c/mL and no 2 consecutive VL ≥50 c/mL	3 (<1%)	1 (<1%)
2b. ≥2 consecutive VLs ≥50 c/mL with at least one VL ≥200 c/mL	0	2[a] (<1%)
Total (all categories)	**14 (4%)**	**25 (7%)**

[a]One participant met CVW criteria by Week 48.

Figure 2. Frequency of Viral Load Blips in Category 1a Participants by Visit Through Week 48



*Percentages were calculated from number of blips in Category 1a participants (Table 1) using post-baseline previously suppressed (<50 c/mL) pt visit Ns respectively for DTG/3TC and DTG + TDF/FTC at: Wk4 (N=355) and (N=362); Wk8 (N=361) and (N=367); Wk 12 (N=362) and (N=376); Wk 24 (N=355) and (N=370); Wk 36 (N=350) and (N=360); Wk 48 (N=348) and (N=351). Numbers on the bottom of each bar represent # of blips at given week visit. Individual participants can have had more than one blip.

- The occurrences of viral blips at each visit by treatment group over 48 weeks were similar (Figure 2)
- The prevalence of archived, pre-existing M184V/I or K65R/E/N was very low (Table 2)
  - No EVLs were observed among these participants
- Through Week 48, the frequency of participants who experienced EVLs with archived major NRTI or INSTI resistance was very low in either treatment group
- In the DTG/3TC group, one participant with archived INSTI mutation mixture Q148Q/R had 2 consecutive VLs between 50 to <200 c/mL during the Week 4 window and a blip at Week 12; the participant withdrew consent and discontinued the study with VL <50 c/mL at the withdrawal visit

Table 2. Summary of Prevalence of Archived Mutations and Participants With Viral Rebound by Pre-existing Resistance at Baseline

Baseline genotypic data available	DTG/3TC (N=322)		TAF-based regimen (N=321)	
Resistance class	**Mutation prevalence[a]**	**Experienced elevated VL[b]**	**Mutation prevalence[a]**	**Experienced elevated VL[b]**
Any major resistance[c]	81 (25%)	5 (2%)	88 (27%)	9 (3%)
No major resistance	241 (75%)	7 (2%)	233 (73%)	13 (4%)
Major NRTI class – any	25 (8%)	1 (<%)	17 (5%)	1 (<%)
M184V or M184I	4 (1%)	0	3 (<1%)	0
K65R or K65E or K65N	0	0	2 (<1%)	0
Any TAM[d]	9 (3%)	0	5 (2%)	0
Other	12 (4%)	1 (<1%)	7 (2%)	1 (<1%)
No M184V/I	318 (99%)	12 (4%)	318 (>99%)	22 (7%)
Major INSTI – any[e]	3 (<1%)	1 (<1%)	5 (2%)	0
Q148Q/R	2 (<1%)	1 (<1%)	1 (<1%)	0
Y143Y/H	0	0	2 (<1%)	0
Y143Y/C	1 (<1%)	0	0	0
R263R/K	0	0	2 (<1%)	0

[a,b]Percentage is based on N – number of participants with baseline proviral DNA genotypic data available from the proviral DNA resistance analysis population (PRAP). PRAP is based on the ITT-E population for whom there are: (1) available proviral DNA genotyping data; (2) at least one post-baseline on-treatment HIV-1 RNA viral load result available; and (3) reason for withdrawal is not protocol deviation. [c]Includes major NRTI, NNRTI, PI, and INSTI resistance-associated mutations based on IAS 2019. [d]TAM – thymidine analogue mutation. [e]Participants with archived major INSTIs all had mixtures of wild-type and specific mutations.

Conclusions

- The occurrences of blips by visit were similar across treatment groups
- All other categories of VL ≥50 c/mL occurred infrequently in all groups, and the occurrences were similar
- The frequency of archived, pre-existing M184V/I or K65R/E/N was very low and did not appear to increase the risk of elevated viral loads in either treatment group, with no participants exhibiting intermittent viremia through Week 48
- In participants with or without pre-existing resistance, intermittent viremia was infrequent
- Switching from a 3-drug TAF-based regimen to a DTG/3TC 2DR was not associated with a higher frequency of intermittent viremia

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Reference: 1. van Wyk J, Ajana F, Bisshop F, et al. Switching to DTG/3TC fixed-dose combination (FDC) is non-inferior to continuing a TAF-based regimen in maintaining virologic suppression through 48 weeks (TANGO study). Presented at: 10th IAS Conference on HIV Science; July 21-24, 2019; Mexico City, Mexico. Slides WEAB0403LB.