# ASSESSING THE VIROLOGIC IMPACT OF ARCHIVED RESISTANCE IN AN HIV-1 SWITCH STUDY TANGO THROUGH WEEK 48

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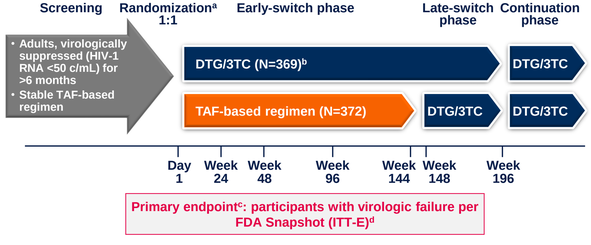
## Introduction

- The TANGO study demonstrated that switching to a 2-drug regimen (2DR) of dolutegravir/lamivudine fixed-dose combination (DTG/3TC FDC) was non-inferior to continuing a tenofovir alafenamide–based 3-drug regimen (3DR) in maintaining virologic suppression in HIV-1–infected, ART-experienced adults through Week 48[1]
- Next-generation sequencing (NGS)-based assay using HIV-1 proviral DNA can detect archived, pre-existing drug resistance in patients with suppressed viral load. The clinical utility of this testing has not been fully determined[2] and testing results should be interpreted with caution[3]
- We performed resistance analyses and assessed the impact of pre-existing, HIV-1 drug resistance on virologic outcomes through Week 48

### 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

- Historic genotypic resistance report is not required for study entry; participants with identified historical IAS major NRTI or INSTI resistance-associated mutations (RAMs) prior to randomization were excluded from the study
- HIV-1 proviral DNA genotyping was conducted retrospectively on baseline whole blood samples from randomized participants per their consent by Monogram Biosciences using GenoSure Archive NGS platform assay that reports resistance mutations at frequencies of ≥15%
- Virologic outcomes based on IAS major NRTI, NNRTI, PI, and INSTI RAMs were determined by last available on-treatment HIV-1 RNA through Week 48 in order to assess pure virologic responses by censoring discontinuations due to non-efficacy reasons. Sensitivity analyses were performed using the FDA Snapshot algorithm at Week 48
- Proviral DNA resistance population (PRAP): based on the intention-to-treat–exposed (ITT-E) population for whom there were available proviral DNA baseline genotypic data; and at least one post-baseline on-treatment HIV-1 RNA viral load (VL) result available; and where reason for withdrawal is not protocol deviation
- The list of major RAMs used in these analyses was based on the IAS 2019 update. Pre-specified INSTI substitutions are listed below (major IAS INSTI mutations are **bolded**):

H51Y, **T66I**/A/K, L68I/V, L74M/I, **E92Q**/V/G, Q95K, T97A, **G118R**, **F121Y**, E138A/K/D/T, G140A/C/S, **Y143C/H/R**/K/S/G/A, P145S, Q146P, **S147G**, **Q148H**/K/R, V151I/L/A, S153F/Y, **N155H**/S/T, E157Q, G163R/K, G193E, S230R, **R263K**

## Results

- With a total of 919 participants screened for the study, 560 (61%) had historic genotypic reports, among those only 9 (1%) participants were excluded from the study due to exclusionary major NRTI resistance:
  - 1 of 9 participants had M41L and D67N, 2 had M41L, and the remaining 6 each had a single mutation identified as M184I, K65R, K219E, K219Q, D67N, and L210W, respectively
- Of treatment-exposed participants, 329/369 (89%) in the DTG/3TC group and 324/372 (87%) in the TAF-based regimen group had proviral DNA genotypes available
- For 734 participant samples tested, 80 (11%) had non-reportable results due to assay failure

### Table 1. Prevalence of Archived Resistance and the Most Frequent Substitutions by Drug Class at Baseline in PRAP*,†

| Resistance class | DTG/3TC (N=322) | TAF-based regimen (N=321) | Total (N=643) |
|---|---|---|---|
| **No major RAMs** | 241 (75%) | 235 (73%) | 476 (74%) |
| **Any major RAMs** | 81 (25%) | 86 (27%) | 167 (26%) |
| **Major NRTI associated** | 25 (8%) | 17 (5%) | 42 (7%) |
| Any TAM[a] | 9 (3%) | 5 (2%) | 14 (2%) |
| A62V | 5 (2%) | 3 (<1%) | 8 (1%) |
| M184V/I[b] | 4 (1%) | 3 (<1%) | 7 (1%) |
| K65N/R[c] | 0 | 2 (<1%) | 2 (<1%) |
| Others[d] | 7 (1%) | 4 (1%) | 11 (2%) |
| **Major NNRTI associated** | 38 (12%) | 52 (16%) | 90 (14%) |
| K103N | 12 (4%) | 17 (5%) | 29 (5%) |
| E138A/K | 14 (4%) | 13 (4%) | 27 (4%) |
| V108I | 5 (2%) | 7 (2%) | 12 (2%) |
| Others[e] | 8 (2%) | 19 (6%) | 27 (4%) |
| **Major PI associated** | 23 (7%) | 20 (6%) | 43 (7%) |
| M46I | 8 (2%) | 7 (2%) | 15 (2%) |
| D30N | 5 (2%) | 2 (<1%) | 7 (1%) |
| Others[f] | 12 (4%) | 12 (4%) | 24 (4%) |
| **Pre-specified INSTI substitutions** | 84 (26%) | 85 (26%) | 169 (26%) |
| **Major INSTI associated** | 3 (<1%) | 5 (1%) | 8 (1%) |
| Q148Q/R | 2 (<1%) | 1 (<1%) | 3 (<1%) |
| Y143Y/H | 0 | 2 (<1%) | 2 (<1%) |
| Y143Y/C | 1 (<1%) | 0 | 1 (<1%) |
| R263R/K | 0 | 2 (<1%) | 2 (<1%) |
| **Other pre-specified INSTI substitutions** | 83 (25%) | 82 (25%) | 165 (26%) |
| G193E | 34 (11%) | 30 (9%) | 64 (10%) |
| L74I | 16 (5%) | 24 (7%) | 40 (6%) |
| V151I | 12 (4%) | 13 (4%) | 25 (4%) |
| E157Q | 9 (3%) | 6 (2%) | 15 (2%) |
| E138D | 4 (1%) | 4 (1%) | 8 (1%) |
| T97A | 5 (2%) | 3 (<1%) | 8 (1%) |
| L74M | 3 (<1%) | 4 (1%) | 7 (1%) |
| Others[g] | 12 (4%) | 7 (2%) | 19 (3%) |

*PRAP: proviral resistance analysis population is described in the Methods section.
†A participant can have more than one mutation. Numerator is the number of participants with a particular mutation or mutation mixture with wild-type detected.
[a]TAMs: thymidine analogue mutations including M41L, D67N, K70R, L210W, T215F/Y, and K219E/Q. [b]Participants with archived M184V or I all had mutation mixtures with wild-type virus. [c]Participants with archived K65N or R all had mutation mixtures with wild-type virus. [d]Other NRTI RAMs detected <1% in total (n): V75I (6), L74V (3), F77L (1), and K70E (1). [e]Other NNRTI RAMs detected <1% in total: K101E (6), Y181C (4), G190A/S (4), V106A/M (4), Y188C/H/L (4), H221Y (3), E138G (2), M230I/L (2), P225H (2), F227C (1), and K103S (1). [f]Other PI RAMs detected <1% in total (n): V82A (5), V82/F/L/S (4), Q58E (4), M46L (3), L90M (2), N88S (2), I47V (1), I50L (1), and N83D (1). [g]Other pre-specified INSTI substitutions detected <1% in total: T66A (5), G163K/R (5), E138K (2), L68V (2), N155S (2), Q95K (2), G140S (1), and H51Y (1).

- The overall prevalence of any archived major RAM across 4 drug classes was 26% in the PRAP (Table 1)
  - Archived NRTI RAMs were observed in 7% of participants and the frequency of M184V/I (1%) and K65N/R (<1%) was low, being detected as mutation mixtures with wild-type virus
  - Major INSTI RAMs were infrequent, being detected in 1% of participants as mutation mixtures with wild-type virus
  - Other pre-specified INSTI substitutions were observed in 26% of participants and the most frequent substitutions were polymorphic G193E, L74I, and V151I
- Baseline characteristics (eg, age, sex, HIV-1 subtype, baseline 3rd agent class, median CD4+ count) were similar between participants with or without any archived RAMs

### Table 2. Virologic Outcomes by Archived Resistance Category Through Week 48 Using Last On-Treatment HIV-1 RNA in PRAP*

| Baseline resistance class | % of participants with last available on-treatment HIV-1 RNA <50 c/mL | |
|---|---|---|
| | DTG/3TC (N=322) | TAF-based regimen (N=321) |
| Overall participants | 100% (322/322) | >99% (319/321) |
| Any major RAMs | 100% (81/81) | 100% (86/86) |
| No major RAMs | 100% (241/241) | >99% (233/235) |
| Any major NRTI RAMs | 100% (25/25) | 100% (17/17) |
| No major NRTI RAMs | 100% (297/297) | >99% (302/304) |
| Any major INSTI RAMs | 100% (3/3) | 100% (5/5) |
| No major INSTI RAMs | 100% (319/319) | >99% (314/316) |
| Any pre-specified INSTI substitutions | 100% (84/84) | 100% (85/85) |
| No pre-specified INSTI substitutions | 100% (238/238) | >99% (234/236) |
| Any major NNRTI RAMs | 100% (38/38) | 100% (52/52) |
| No major NNRTI RAMs | 100% (284/284) | >99% (267/269) |
| Any major PI RAMs | 100% (23/23) | 100% (20/20) |
| No major PI RAMs | 100% (299/299) | >99% (299/301) |

*PRAP is described in the Methods section.
All *P* values based on Fisher's exact test for the comparison of the proportions of participants with HIV-1 RNA <50 c/mL at Week 48 (within treatment group comparison for subgroup with class resistance vs subgroup without class resistance) were >0.99 for the TAF-based regimen group and non-calculable in the DTG/3TC group due to 100% response rates in both subgroups across all resistance classes.

- Through Week 48, 322/322 (100%) participants on DTG/3TC and 319/321 (>99%) on a TAF-based regimen were virologically suppressed (Table 2)
  - All participants with major NRTI, INSTI, NNRTI, or PI RAMs were suppressed
    - Including 4 with archived M184V/I on DTG/3TC
- No participants in the DTG/3TC group met protocol-defined confirmed virologic withdrawal (CVW) criteria through Week 48 and one participant in the TAF-based regimen group without any archived major RAMs met CVW criteria with no emergent resistance
- Frequency of viral rebound (VL ≥50 c/mL) at post-baseline visits was low among participants with archived major NRTI or INSTI RAMs through Week 48[4]
  - No viral rebound was observed for participants with archived M184V/I or K65N/R

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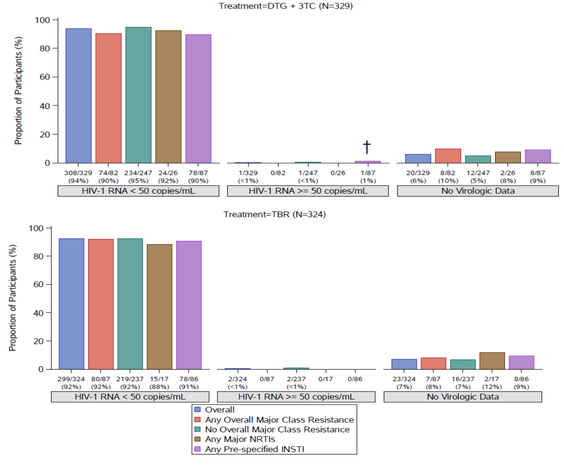
### Figure 2. Treatment Response at Week 48 by Archived Resistance Class – Snapshot Sensitivity Analysis in PRSAP*




*PRSAP: ITT-E population for all participants with available proviral baseline genotypic data.
†One participant with pre-specified INSTI substitution L74I had an early withdrawal with the last on-study VL of 507 c/mL at Week 8 due to a protocol deviation of non-compliance.

- Irrespective of presence of major RAMs, similar high suppression rates were observed across both treatment groups using the FDA Snapshot endpoint (Figure 2)

## Discussion

- In the TANGO study, archived resistance identified via proviral DNA testing on participants with no known resistance or a history of virologic failure was not associated with virologic outcomes at Week 48. Due to high virologic efficacy rates observed in the TANGO study, the utility of proviral DNA testing in similar patients in a clinical setting may be of limited value

## Conclusions

- In the TANGO study, the prevalence of archived, pre-existing resistance detected by proviral DNA genotyping to ARVs was consistent with recent findings by others[3,5]
- Archived major NRTI RAMs (eg, M184V/I, K65N/R, and TAMs) and INSTI RAMs (eg, Q148R, Y143C/H, R263K) were infrequent
- High rates of virologic suppression were maintained in participants in both treatment groups through Week 48
- The presence of archived major RAMs did not impact virologic outcomes through Week 48
  - For participants with any major RAMs across 4 drug classes, 100% of participants in both treatment groups had HIV-1 RNA <50 c/mL at their last on-treatment study visit

**References: 1.** van Wyk et al. *Clin Infect Dis.* 2020 [Epub ahead of print]. **2.** DHHS. 2018. **3.** Günthard et al. *Clin Infect Dis.* 2019;68:177-187. **4.** Wang et al. EACS 2019; Basel, Switzerland. Poster PE3/15. **5.** McClung et al. CROI 2019; Seattle, WA. Abstract 3337.