# DTG + 3TC VS DTG + TDF/FTC (GEMINI-1 & -2): CONFIRMED VIROLOGIC WITHDRAWALS (CVWs) THROUGH WEEK 96

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**Presenting on behalf of the authors.*

## Introduction

- In the primary analysis of the GEMINI-1 & -2 studies at Week 48, the 2-drug regimen (2DR) of dolutegravir (DTG) + lamivudine (3TC) was non-inferior to the 3-drug regimen (3DR) of DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in HIV-1–infected, ART-naive adults, leading to the approval of the 2DR as a once-daily single-tablet regimen by the US FDA and the EMA[1]
- At the 96-week analysis, non-inferiority was maintained[2]
- 11 participants on 2DR and 7 on 3DR met protocol-defined confirmed virologic withdrawal (CVW) criteria through Week 96
- We present a detailed description of these CVWs

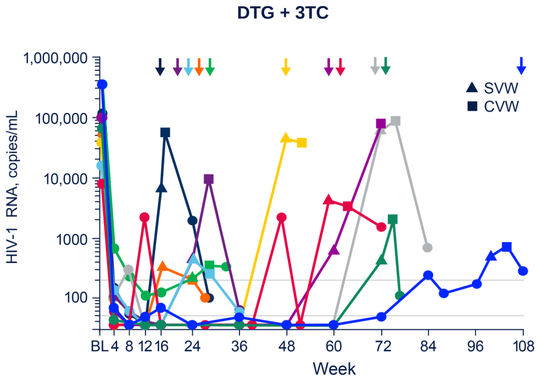
## Methods

- Treatment-naive adults were eligible if screening HIV-1 RNA viral loads (VLs) were between 1000-500,000 c/mL, HIV-1 genotype showed no major RT/PR resistance mutations, and were HBV negative
- CVW was defined as 2 consecutive VLs (suspected virologic withdrawal [SVW] result followed by CVW result) meeting virologic non-response (VL ≥200 c/mL after Week 24 or <1.0 log decline in VL by Week 12 unless HIV-1 RNA is <200 c/mL) or virologic rebound criteria (≥200 c/mL after prior confirmed suppression to <200 c/mL)
- Monogram Biosciences performed integrase and RT/PR genotypic and phenotypic resistance testing on Day 1 and SVW samples
- We evaluated CVW participant baseline (BL) VL and CD4+ cell count characteristics, resistance, VL progression, potential adherence issues, and study drug interruption (based on investigator reporting) through the study course

## Results

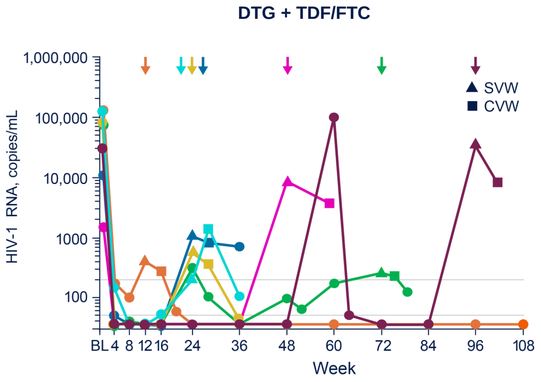
- In GEMINI-1 & -2, of 1974 participants screened, 3 (0.15%) failed screening due to transmitted M184V resistance
- Overall, 11 participants on DTG + 3TC and 7 on DTG + TDF/FTC met CVW criteria through Week 96
- All CVWs experienced virologic rebound, 2 CVWs in each arm experienced at least one VL elevation ≥200 c/mL after suppression to <50 c/mL and none of the 18 CVWs had VL blips (defined as a single VL between ≥50 to <200 c/mL with adjacent values <50 c/mL) that preceded CVW
  - One DTG + 3TC participant did not achieve suppression prior to withdrawal at Week 24 (Figures 1 and 2)

**Figure 1. Individual HIV-1 RNA Viral Load Progression by Visit for Participants Meeting CVW Criteria in the DTG + 3TC Arm**




Arrows represent the week in which CVW occurred. The color of the arrow corresponds to the color assigned to each participant.

**Figure 2. Individual HIV-1 RNA Viral Load Progression by Visit for Participants Meeting CVW Criteria in the DTG + TDF/FTC Arm**




Arrows represent the week in which CVW occurred. The color of the arrow corresponds to the color assigned to each participant.

- There were low and comparable CVWs across treatment arms by baseline VL or CD4+ cell count (Table 1)

**Table 1. CVWs by Baseline CD4+ Cell Count and Baseline HIV-1 RNA**

| Baseline subgroups | | DTG + 3TC | DTG + TDF/FTC |
|---|---|---|---|
| BL CD4+ cell count, % (n/N) | ≤200 cells/mm$^3$ | 4.8 (3/63) | 3.6 (2/55) |
| | >200 cells/mm$^3$ | 1.2 (8/653) | 0.8 (5/662) |
| BL HIV-1 RNA, % (n/N) | ≤100,000 c/mL | 1.0 (6/576) | 0.7 (4/564) |
| | >100,000 c/mL | 3.6 (5/140) | 2.0 (3/153) |

**Table 2. Summary of CVWs in DTG + 3TC Arm**

| Participant | Sub-type | BL CD4+ (cells/mm$^3$) | CVW visit (week) | BL VL (c/mL) | SVW VL (c/mL) | CVW VL (c/mL) | WD VL (c/mL) | Adherence/ treatment interruption |
|---|---|---|---|---|---|---|---|---|
| A | BF | 212 | W16 | 124,492 | 6648 | 56,435 | 95 | Unknown |
| B | B | 284 | W24 | 50,263 | 348 | 206 | 96 | Adherent |
| C | B | 529 | W24 | 17,232 | 461 | 251 | 59 | Unknown |
| D | B | 213 | W24 | 96,277 | 451 | 9602 | 67 | Treatment interruption |
| E | F | 19 | W24 | 368,439 | 212 | 376 | 362 | Adherent |
| F | B | 414 | W48 | 37,701 | 43,908 | 38,457 | ND | Unknown; concurrent SAE (psychosis) |
| G | B | 567 | W60 | 7654 | 3972 | 3131 | 1513 | Non-adherent |
| H | B | 347 | W60 | 101,671 | 703 | 85,556 | ND | Treatment interruption |
| I | B | 50 | W72 | 63,817 | 422 | 2154 | 115 | Non-adherent |
| J | B | 74 | W72 | 112,812 | 61,076 | 87,794 | 671 | Non-adherent |
| K* | B | 317 | W96 | 341,818 | 396 | 726 | 280 | Non-adherent |

*Participant K SVW visit occurred within the Week 96 window for the Snapshot analysis. WD, withdrawal.

**Table 3. Summary of CVWs in DTG + TDF/FTC Arm**

| Participant | Sub-type | BL CD4+ (cells/mm$^3$) | CVW visit (week) | BL VL (c/mL) | SVW VL (c/mL) | CVW VL (c/mL) | WD VL (c/mL) | Adherence/ treatment interruption |
|---|---|---|---|---|---|---|---|---|
| L* | B | 22 | W12 | 136,753 | 393 | 276 | NA | Unknown |
| M | B | 226 | W24 | 10,930 | 1136 | 809 | 647 | Unknown |
| N | B | 251 | W24 | 76,325 | 569 | 362 | 46 | Unknown |
| O | B | 201 | W24 | 156,701 | 213 | 1559 | 97 | Unknown |
| P | B | 602 | W48 | 1568 | 8384 | 3653 | 3011 | Unknown |
| Q | B | 253 | W72 | 66,881 | 254 | 232 | 121 | Unknown |
| R | B | 144 | W96 | 28,905 | 30,316 | 7793 | ND | Non-adherent |

*Participant L met CVW criteria at Week 12; not withdrawn from study due to central laboratory data reporting error and continued to remain suppressed to Week 108. WD, withdrawal.

### Resistance Analysis

- Resistance data to determine treatment emergence were available for all samples except 2 cases on DTG + TDF/FTC where testing failed with HIV-1 VL below the assay cut-off. No treatment-emergent genotypic or phenotypic resistance in IN or RT was observed in any CVWs on either treatment arm
- All fold change (FC) at withdrawal visit were below the Monogram phenotypic clinical or biological cut-offs. Maximum FC at withdrawal was 1.13 and 1.74 for DTG and 3TC, respectively, for CVWs in the DTG + 3TC arm, and 1.38, 1.07, and 1.28 for DTG, TDF, and FTC for CVWs, respectively, in the DTG + TDF/FTC arm
- For participants with VLs at withdrawal, VL decreased ≥2 fold for 8 of 9 participants in the DTG + 3TC arm and 3 of 5 in the DTG + TDF/FTC arm between the CVW and withdrawal time points (Tables 2 and 3)
- 6/11 CVWs in the DTG + 3TC arm and 1/7 in the DTG + TDF/FTC arm appeared to be associated with adherence or treatment interruption issues

## Conclusions

- In GEMINI-1 & -2, there were low and comparable numbers of participants meeting CVW criteria through 96 weeks in the DTG + 3TC and DTG + TDF/FTC arms with low and comparable CVWs across treatment arms by baseline VL or CD4+ cell count
- There was no emergent genotypic or phenotypic resistance to INI or NRTIs observed through 96 weeks among CVWs
- VL progressions for CVWs generally show a steep increase in viral load followed by a decrease at withdrawal visit, consistent with non-adherence/ treatment interruption and subsequent re-adherence
- These data further support the durability and high barrier to resistance of the 2DR DTG + 3TC

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**References:**
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