DTG + 3TC IN GEMINI-1 & -2: HIV-1 REPLICATION AT <50 C/ML AND VL 'BLIPS' THROUGH 144 WEEKS

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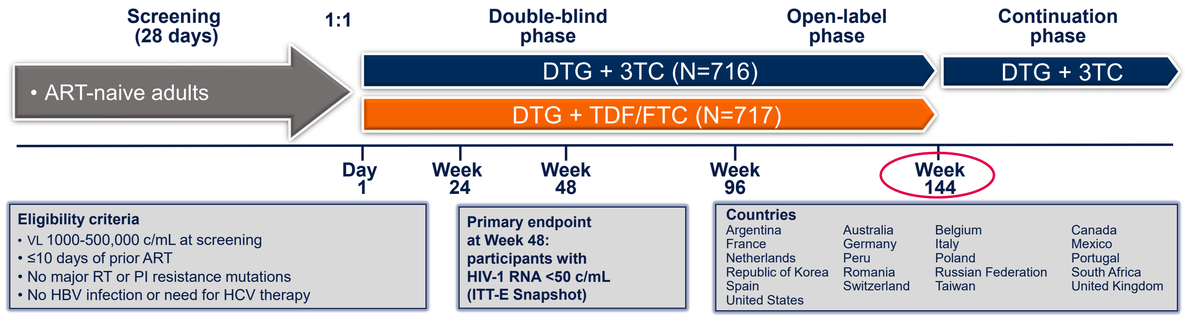
Introduction

- The GEMINI-1 & -2 studies in treatment-naive adults (Figure 1) showed DTG + 3TC was non-inferior to DTG + TDF/FTC by FDA Snapshot (HIV-1 RNA <50 c/mL) at Week 144.[1]
  - HIV-1 RNA <50 c/mL was also comparable across baseline subgroups including HIV-1 RNA > or ≤100,000 c/mL and CD4+ cell count > or ≤200 cells/mm^3.
- Abbott's RealTime HIV-1 assay provides quantitative viral load (VL) from 40 to 10,000,000 c/mL, and qualitative target detected (TD) or target not detected (TND) for VL <40 c/mL.
- In this post hoc analysis, we assessed very-low-level viremia by TND and TD, and low-level quantitative viral replication including 'blips' through Week 144 overall, and by baseline stratification subgroups.

Figure 1. GEMINI-1 and GEMINI-2 Study Design

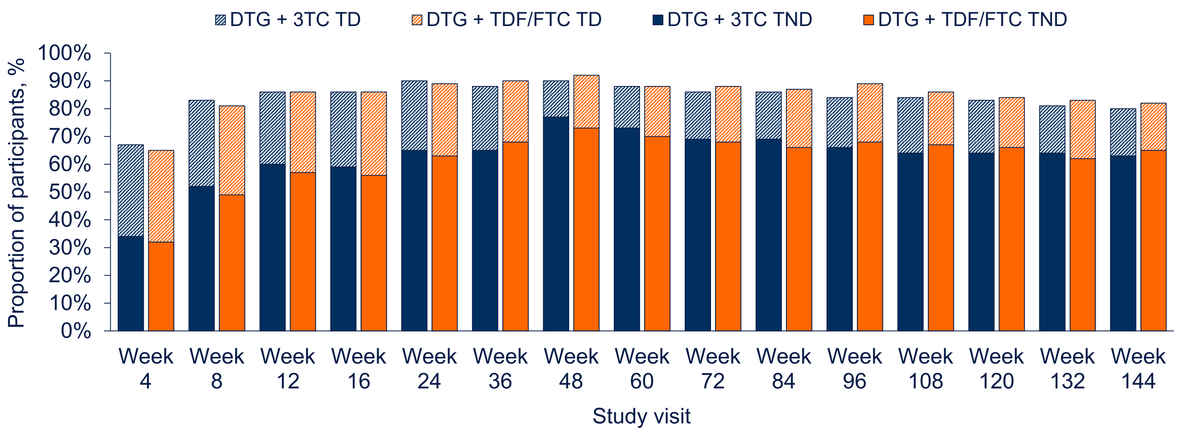


TND

Methods and Assessments

- The proportion of participants with VL <40 c/mL and TND status throughout Week 144 is presented based on Snapshot analysis via a Cochran-Mantel-Haenszel stratified analysis, adjusting for the following baseline stratification factors:
- Plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) and CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3) and Study (204861 vs 205543).
- Participant subgroups assessed included the ITT-E population and an Observed subpopulation (ITT-E participants with VL <50 c/mL at Week 144).
- Participants with VL ≥50 c/mL were assigned to mutually exclusive VL groups as previously presented.[2] Those with no VL ≥200 c/mL could have a single VL between 50 to <200 c/mL with adjacent values <50 c/mL ('blip' definition) or ≥ two consecutive VLs between 50 to <200 c/mL. Those with ≥1 VL ≥200 c/mL could meet SVW criteria with a single occurrence or meet CVW criteria with consecutive VL ≥200 c/mL.

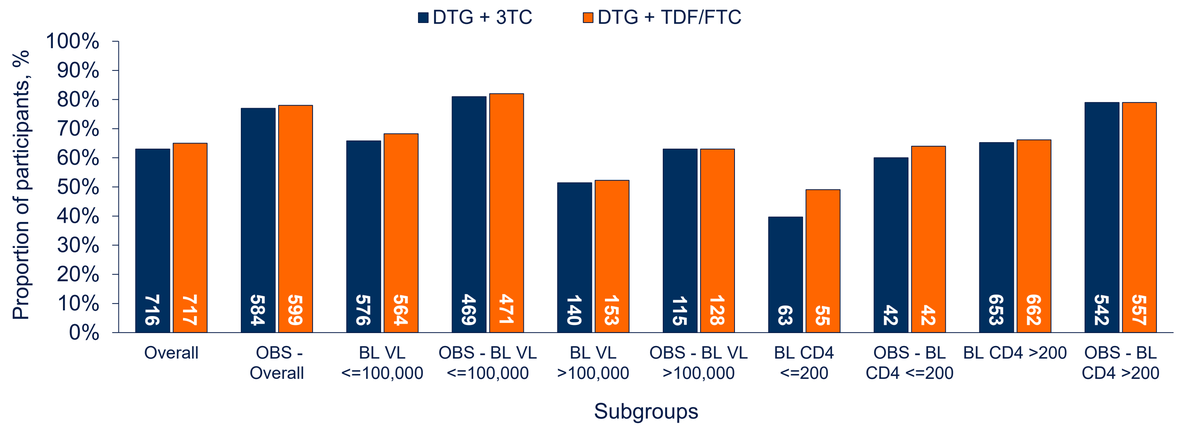
Figure 2. Participant Proportions* With TND or TD Were Similar Across Arms From Week 4 Through Week 144, ITT-E Population



*Percentages calculated for DTG + 3TC and DTG + TDF/FTC in Fig. 2 used, respectively, N=716 and N=717 ITT-E population as denominators.

- Proportions with TND trended upward through ~Week 48 and were similar between arms at all visits.
- The proportions that had highest TD occurred in earlier visits and decreased to stabilize around Week 48.

Figure 3. Proportions* of Participants With TND by BL Subgroups Were Similar Across Arms for ITT-E (Overall) and Observed (OBS) Populations at Week 144



*Percentages calculated for DTG + 3TC and DTG + TDF/FTC in Fig. 3 used ITT-E Overall or Observed and HIV-1 RNA and CD4 subgroups as denominators, which are in white overlaid on vertical bars.

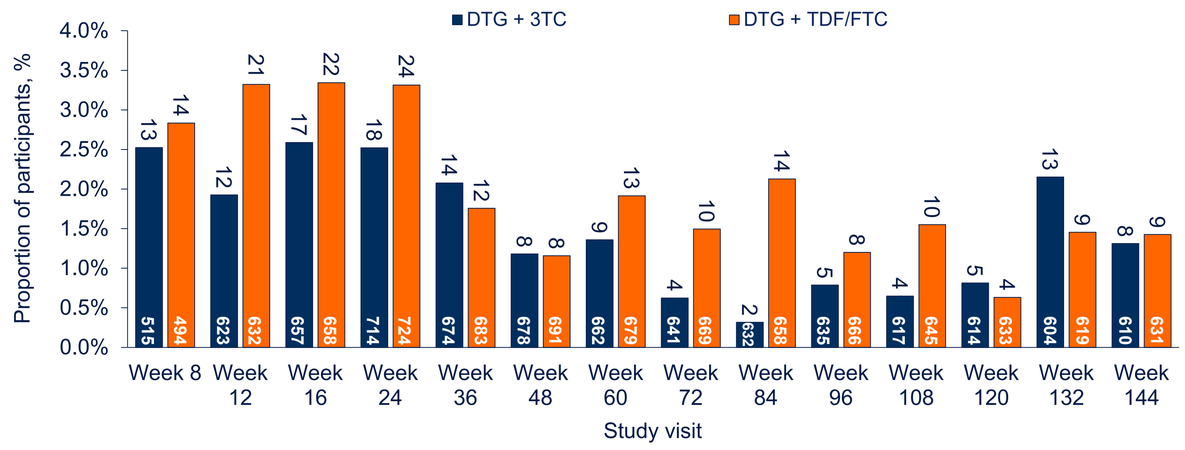
- At Week 144, there were similar proportions of ITT-E Overall participants with TND receiving DTG + 3TC vs DTG + TDF/FTC by Snapshot (63% [451/716] vs 65% [465/717]), or for Observed (OBS) population (77% [451/584] vs 78% [465/599]).
- Proportions with TND within subgroups were generally similar between arms.
- For the ITT-E Overall group, the largest difference was seen with BL CD4 ≤200.
  - Proportion with TND was 40% for the DTG + 3TC arm compared with 49% for the DTG + TDF/FTC arm, though the Ns were very small, at 25/63 and 27/55, respectively.
  - For the Observed population, the difference in proportions with TND seen with BL CD4 ≤200 was smaller at 60% vs 64%, with Ns of 25/42 and 27/42, respectively.

'Blips'

Methods and Assessments

- 'Blips' by visit were assessed from Day 1 after VL suppression to <50 c/mL, and from Weeks 48 through 144. Percentages are based on number of 'blips' and available VLs in the analysis window. Multiple VLs from the same visit week are included, if applicable. Participants who never suppressed, or VL records before and including the first suppression <50 c/mL, are excluded.

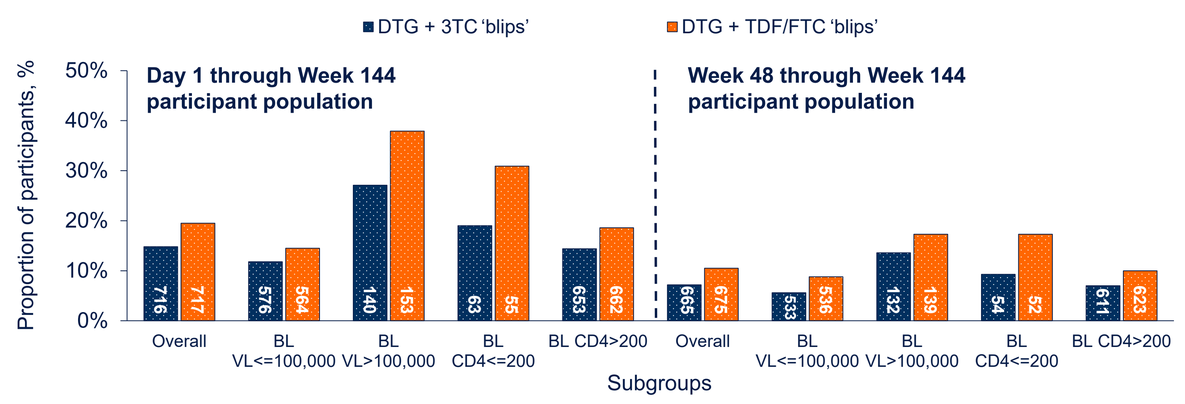
Figure 4. Participant Proportions* With 'Blips' Were Similar Across Arms by Visit Through Week 144, ITT-E Population



*The denominator is in white overlaid on the vertical bars and is the total number of observations from all participants with data for the specified visit window. Numbers on tops of bars are # of 'blips' at given week visits. Note that individual can have had more than one 'blip' (see Table 1).

- 'Blip' proportions were higher early and decreased around Weeks 36 to 48.
- The proportion of 'blips' was generally numerically lower for DTG + 3TC but similar across arms through Week 144.

Figure 5. Participant Proportions* With ≥1 'Blip' From Day 1 to Week 144 or Week 48 to Week 144 by BL Subgroups Were Generally Similar Across Arms



*Percentages calculated for DTG + 3TC and DTG + TDF/FTC in Fig. 5 use ITT-E or subgroup Ns (by BL VL or CD4) as denominators shown in white on columns.

- There was a broadly lower 'blip' frequency from Week 48 through Week 144, ie, after participants had suppressed.
- The highest 'blip' proportion was observed for the Day 1 to Week 144 category in DTG + TDF/FTC participants with BL VL >100,000 c/mL or CD4+ ≤200 cells/mm^3.

Table 1. Participants With Different Numbers of 'Blips' From Day 1 to Week 144

'Blips' per participant	DTG + 3TC (%)	DTG + TDF/FTC (%)
1	83 (11.6%)	111 (15.5%)
2	20 (2.8%)	23 (3.2%)
3	3 (0.4%)	4 (0.6%)
4	0	1 (0.1%)
5	0	1 (0.1%)
Total	**106 (14.6%)**	**140 (19.5%)**

*Percentages calculated for DTG + 3TC and DTG + TDF/FTC, respectively, used N=716 and N=717 ITT-E population as denominators.

- Most participants with 'blips' had only 1, and this number was lower in the DTG + 3TC arm.
- No 'blips' were observed for participants meeting CVW criteria in either arm.

Discussion

- Two-drug regimens (2DRs) reduce the number of drugs for PLWH who need lifelong ART.[3]
- The implications of low-level qualitative HIV-1 replication (TD and TND) remain exploratory, and without known or apparent clinical consequences. Previously reported assessments of very-low-level TND and TD for qualitative HIV-1 RNA <40 c/mL for the GEMINI studies at Week 48[4] showed similar frequency of participants across arms with undetectable HIV-1 RNA, although the median time to undetectable HIV-1 RNA was numerically shorter for DTG + 3TC participants vs DTG + TDF/FTC participants with BL VLs >100,000 c/mL.
- Low-level single HIV-1 VL elevations known as 'blips' (HIV-1 RNA of 50-200 c/mL preceded and followed by HIV-1 RNA <50 c/mL) are generally considered as clinically not impactful.[5] As previously reported,[2] 'blip' assessments for the GEMINI studies at Week 48 showed proportion with 'blips' through 48 weeks was overall similar between the DTG + 3TC and DTG + TDF/FTC arms, though a higher percentage of 'blips' occurred in participants receiving DTG + TDF/FTC than DTG + 3TC if BL VL was >100,000 c/mL.

Conclusions

- Proportions of participants with TND were similar through Week 144 in the DTG + 3TC and DTG + TDF/FTC arms.
  - For participants with BL CD4+ cell count ≤200 cells/mm^3, the difference in TND proportion for DTG + 3TC vs DTG + TDF/FTC was smaller for the Observed population compared with the ITT-E population.
- The frequency of 'blips' through Week 144 was generally similar across arms when assessed early from Day 1 or from Week 48.
- These data continue to demonstrate the efficacy, potency, and durability of the DTG + 3TC 2DR in treatment-naive adults.

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References: 1. Cahn et al. HIV Glasgow 2020; Virtual. Poster P018. **2.** Underwood et al. IAS 2019; Mexico City, Mexico. Poster MOPEB231. **3.** Kelly et al. *Drugs.* 2016;76:523-531. **4.** Underwood et al. CROI 2019; Seattle, WA. Abstract 490. **5.** Panel on Antiretroviral Guidelines for Adults and Adolescents. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed June 16, 2021. See page F3, *Managing Transient Viremia, or 'Blips.'*

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