HIV Replication at <40 c/mL for DTG + 3TC vs DTG + TDF/FTC in the GEMINI-1 & -2 Studies

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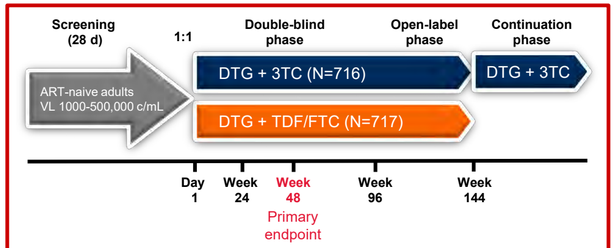
Introduction

- The GEMINI-1 and -2 studies in treatment-naive adults with screening HIV-1 RNA ≤500,000 c/mL showed dolutegravir + lamivudine (DTG + 3TC, 2DR) was non-inferior to DTG + tenofovir disoproxil fumarate/ emtricitabine (DTG + TDF/FTC, 3DR) at Week 48 by FDA Snapshot algorithm; 91% (655/716) in the 2DR arm vs 93% (669/717) in the 3DR arm achieved HIV-1 RNA <50 c/mL.[1]
- Low rates of virologic withdrawal were observed at Week 48 in both the DTG + 3TC and DTG + TDF/FTC arms; respectively, 6 and 4 participants met these criteria in the DTG + 3TC and DTG + TDF/FTC arms, and no participants in either arm had treatment-emergent INSTI or NRTI mutations.[1]
- Abbott RealTime HIV-1 assay used in the studies measures viral load (VL) from 40 to 10,000,000 c/mL, and provides qualitative target detected (TD) or target not detected (TND) for VL <40 c/mL.
- Clinical and subject management implications of more stringent low-level VL data need clarification. We assessed the proportion of participants with TND over time and by baseline (BL) VL for 2DR vs 3DR.

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



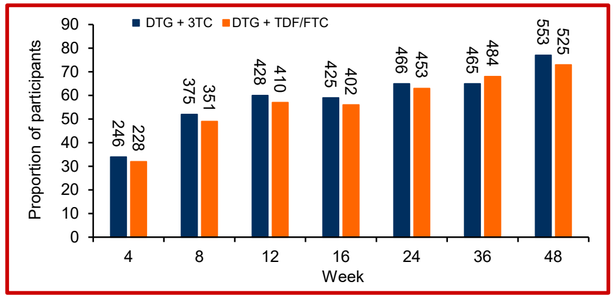
Identically designed, randomised, double-blind, parallel-group, multicentre, non-inferiority studies.

Methods

- Participants were randomised 1:1 to treatment with 2DR or 3DR. The proportion of participants with HIV-1 RNA <40 c/mL and TND status at Week 48 was analysed using a Cochran-Mantel-Haenszel test stratified by plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) at BL and study.
- Proportion of participants with HIV-1 RNA <40 c/mL and TND status were summarised by visit and at Week 48 by BL HIV-1 RNA subgroup. Time to TND status overall and by BL HIV-1 RNA subgroup were estimated using non-parametric Kaplan-Meier method.

Results

Figure 2. Proportion of Participants With TND by Visit: Snapshot Analysis



- At Week 48, similar proportions of participants had Snapshot TND in the 2DR and 3DR arms (77% [553/716] vs 73% [525/717]; adjusted difference, 3.8%; 95% CI, −0.6% to 8.2%).
- Proportions were also similar at Weeks 4 (34% vs 32%), 8 (52% vs 49%), 12 (60% vs 57%), 16 (59% vs 56%), 24 (65% vs 63%), and 36 (65% vs 68%).

Table 1. Proportion of Participants With TND at Week 48 (Snapshot Analysis) by Baseline Plasma HIV-1 RNA Levels

Baseline VL strata (c/mL)	DTG + 3TC n/N (%)[a]	DTG + TDF/FTC n/N (%)[a]	Treatment difference (95% CI)[b]
≤100,000	**463/576 (80)**	**446/564 (79)**	**1.3 (−3.4 to 6.0)**
>100,000	**90/140 (64)**	**79/153 (52)**	**12.7 (1.4 to 23.9)**
>250,000	25/51 (49)	20/46 (43)	5.5 (−14.3 to 25.4)
>400,000	5/18 (28)	6/24 (25)	2.8 (−24.2 to 29.8)

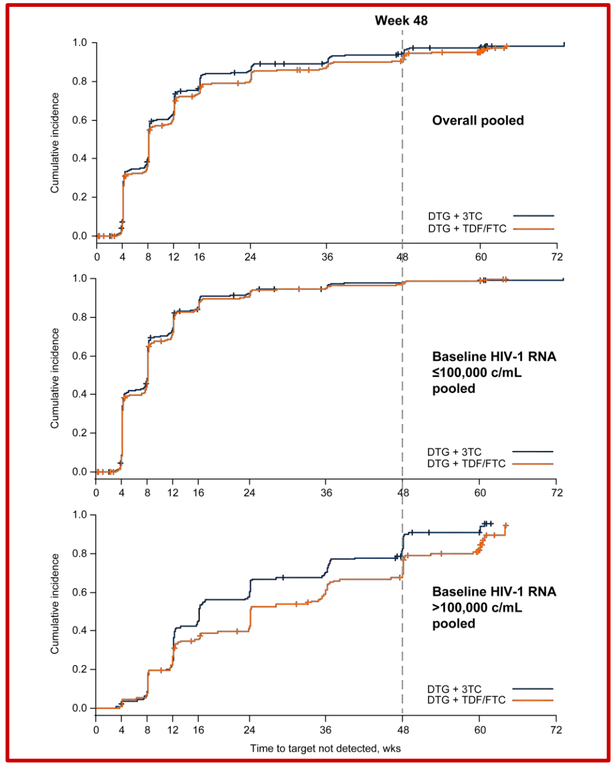
[a]Number responded/Number assessed (%). [b]Unadjusted proportion of DTG + 3TC − proportion of DTG + TDF/FTC (95% CI).

- Responses to TND were similar for participants with BL VL ≤100,000 c/mL.
- Responses to TND were numerically higher for 2DR vs 3DR arms for participants with BL VL >100,000 c/mL. By study:
  - GEMINI-1 response to TND: 2DR = 51/74 (69) and 3DR = 34/76 (45).
  - GEMINI-2 response to TND: 2DR = 39/66 (59) and 3DR = 45/77 (58).

Kaplan-Meier Time to Suppression (Plasma HIV-1 RNA <50 c/mL)

- Median time to HIV-1 RNA <50 c/mL was 29 days for both arms when BL VL ≤100,000 c/mL and 57 days for both arms when BL VL >100,000 c/mL.

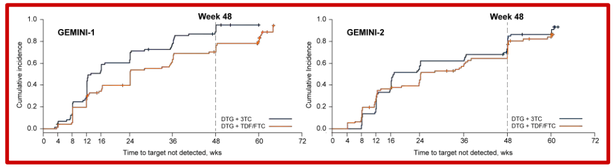
Figure 3. Kaplan-Meier Plots of Time to TND: Overall Participants and by Baseline HIV-1 RNA Subgroup



Participants with HIV-1 RNA <40 c/mL and missing interpretation for Target Detected (TD)/ Target Not Detected (TND) status are assumed to be TD.

- Overall, median (95% CI) time to TND was 57 (NE, NE) days for 2DR vs 57 (57, 58) days for 3DR.
- For the BL ≤100,000 c/mL stratum, median (95% CI) time to TND was 57 (56, 57) days for both 2DR and 3DR.
- For the BL >100,000 c/mL stratum, median (95% CI) time to TND was shorter for 2DR at 113 (88, 168) days vs 169 (168, 248) days for 3DR.

Figure 4. Kaplan-Meier Plots of Time to TND: By Baseline HIV-1 RNA >100,000 c/mL for GEMINI-1 and GEMINI-2



- GEMINI-1 median (95% CI) time to TND: 2DR = 93 (85, 168) days; 3DR = 169 (115, 252) days.
- GEMINI-2 median (95% CI) time to TND: 2DR = 118 (113, 169) days; 3DR = 169 (133, 256) days.

Discussion

- The suppression of HIV-1 RNA VL in plasma is overall recognised as predictive of antiretroviral regimen success and when elevated may predict HIV evolution and emergence of resistance.[2]
- More sensitive measures of HIV-1 RNA levels for patient management are exploratory. Additional analyses of low-level qualitative or quantitative HIV-1 RNA may be useful for optimising treatment/patient management.

Conclusions

- Similar proportions of participants in the DTG + 3TC and DTG + TDF/FTC arms had TND by Snapshot at all weeks.
- Snapshot response rates based on TND status at Week 48 were similar between arms for the BL ≤100,000 c/mL subgroup and numerically higher for DTG + 3TC in the BL >100,000 c/mL subgroup.
- Median time to TND was similar overall and in the BL VL ≤100,000 c/mL subgroup and less for DTG + 3TC vs DTG + TDF/FTC if >100,000 c/mL at BL.
- These data, utilising a more stringent but exploratory TND Snapshot criterion, continue to demonstrate the effectiveness and potency of DTG + 3TC in treatment-naive participants.

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References: 1. Cahn et al. *Lancet*. 2019;393:143-155. **2.** Ryscavage et al. *Antimicrob Agents Chemother*. 2014;58:3585-3598.