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-naïve adults with screening HIV-1 RNA ≤50,000 c/mL showed dolutegravir + tenofovir disoproxil fumarate/emtricitabine (DTG + TDF; 2DR) was inferior to DTG + tenofovir disoproxil fumarate/emtricitabine/efavirenz (DTG + TDF/FTC; 3DR) at Week 48 by FDA Snapshot algorithm (81%, 655/716) in the DTG arm vs 93% (655/717) in the 3DR arm, achieved HIV-1 RNA <50 c/mL.

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 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.

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: proportion of participants with TND overall and by baseline VL subgroup:
  - Baseline VL ≤100,000 c/mL: 2DR = 93 (85, 168) days; 3DR = 97 (63, 168) days.
  - Baseline VL >100,000 c/mL: 2DR = 93 (85, 168) days; 3DR = 97 (63, 168) days.

- GEMINI-2: proportion of participants with TND overall and by baseline VL subgroup:
  - Baseline VL ≤100,000 c/mL: 2DR = 93 (85, 168) days; 3DR = 97 (63, 168) days.
  - Baseline VL >100,000 c/mL: 2DR = 93 (85, 168) days; 3DR = 97 (63, 168) days.

- GEMINI-1 and -2 median (95% CI) time to TND: 2DR = 93 (85, 168) days; 3DR = 97 (63, 168) days.
  - Overall, median (95% CI) time to TND was 37 (36, 38) days for both 2DR and 3DR.
  - Median time to TND was similar overall and in the BL ≤100,000 c/mL subgroup and for less than for DTG + 3TC vs DTG + TDF/FTC at ≥100,000 c/mL at BL.

These data, utilising a more stringent but exploratory TND Snapshot algorithm; 91% (655/716) in the 2DR arm vs 93% (669/717) in the 3DR arm achieved HIV-1 RNA <50 c/mL.

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.

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, 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 overall and by baseline (BL) VL for 2DR vs 3DR.

Results
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 (19% vs 25%), 12 (52% vs 49%), 24 (85% vs 63%), and 36 (85% vs 66%).

Similar proportions of participants in the DTG + 3TC and DTG + 12.7 (1.4 to 23.9)

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.

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 in the BL ≤100,000 c/mL subgroup and less for DTG + 3TC vs DTG + TDF/FTC at >100,000 c/mL at BL.

These data, utilising a more stringent but exploratory TND SnapShot cutoff, continue to demonstrate the effectiveness and potency of DTG + 3TC in treatment-naïve participants.