IMPACT OF TREATMENT ADHERENCE ON EFFICACY OF DTG + 3TC AND DTG + TDF/FTC: POOLED WEEK 144 ANALYSIS OF THE GEMINI-1 AND GEMINI-2 CLINICAL STUDIES

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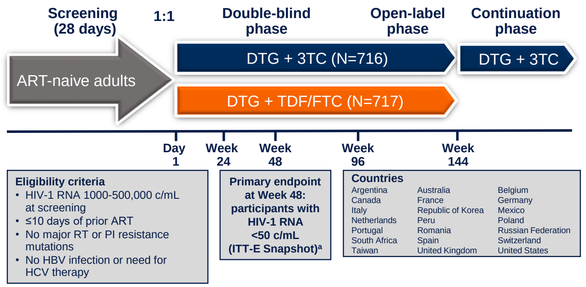
Introduction

- High adherence to ART is associated with increased rates of virologic suppression[1]
  - Regimen "forgiveness," or the ability to achieve or maintain virologic suppression despite suboptimal adherence, is an important measure of potency and durability
- DTG-based 3-drug regimens have demonstrated high rates of virologic suppression in treatment-naive adults with lower adherence levels (ie, <95%)[2]
- In the GEMINI-1 (NCT02831673) and GEMINI-2 (NCT02831764) trials, the 2-drug regimen (2DR) DTG + 3TC was non-inferior to the standard 3-drug regimen (3DR) DTG + TDF/FTC in achieving HIV-1 RNA <50 c/mL in treatment-naive adults at Weeks 48, 96, and 144[3-5]
  - At Week 48, lower treatment adherence (<90%) resulted in lower but comparable efficacy in both treatment groups[6]
- This post hoc analysis evaluated the impact of treatment adherence on efficacy after 144 weeks of DTG + 3TC vs DTG + TDF/FTC in GEMINI-1 and GEMINI-2

Methods

- GEMINI-1 and GEMINI-2 are double-blind (to Week 96, open-label thereafter), phase III, non-inferiority trials evaluating the efficacy and safety of DTG + 3TC vs DTG + TDF/FTC in treatment-naive adults with HIV-1 (Figure 1)[3]

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



[a]–10% non-inferiority margin for individual studies.

- Percent adherence was calculated as the number of pills taken (the difference between the number of pills available and the number of pills returned) per number of pills prescribed estimated using pill count data
- Participants were categorized by ≥90% vs <90% adherence
- Proportion with HIV-1 RNA <50 c/mL was assessed using Snapshot (missing/switch/discontinuation = failure) and last on-treatment viral load (not accounting for discontinuations for non-virologic reasons) for which adherence could be derived
- The Clopper-Pearson exact method was used to calculate the 95% CIs for the proportion of participants with HIV-1 RNA <50 c/mL within treatment groups in each adherence category

Results

- In each treatment group, 5% of participants had <90% adherence through Week 144
- For this analysis, <10% of participants were missing pill count data

Participant Characteristics

- Demographics and baseline characteristics of participants in GEMINI-1 and GEMINI-2 were well balanced between treatment groups (Table 1)[3-5]

Table 1. Demographics and Baseline Characteristics in GEMINI-1 and GEMINI-2 (ITT-E Population)

Demographic/Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32 (18-72)	33 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	90 (13)	71 (10)
Asian	71 (10)	72 (10)
White	484 (68)	499 (70)
Other	71 (10)	75 (10)
Ethnicity, n (%)		
Hispanic/Latino	215 (30)	232 (32)
Not Hispanic/Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
>100,000, n (%)[a]	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
≤200, n (%)	63 (9)	55 (8)

[a]2% of participants in each group had baseline HIV-1 RNA ≥500,000 c/mL and were included in the ITT-E analysis.

- Baseline HIV-1 RNA and CD4+ cell counts were comparable across adherence categories (Table 2)

Table 2. Adherence Results and Baseline Characteristics (ITT-E Population)

Adherence results	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Adherence category, n (%)[a]		
<90%	35 (5)	34 (5)
≥90%	679 (95)	677 (94)
Baseline HIV-1 RNA by adherence category, median (range), log_{10} c/mL		
<90%	4.48 (2.93-5.75)	4.48 (3.61-5.88)
≥90%	4.43 (1.59-6.27)	4.48 (2.11-6.37)
Baseline CD4+ cell count by adherence category, median (range), cells/mm^3		
<90%	450 (19-1399)	414 (25-884)
≥90%	426 (19-1364)	442 (19-1497)

[a]Adherence categories only include participants with derived study drug adherence data.

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Impact of Adherence

- By both ITT-E Snapshot and last on-treatment viral load analyses, the proportion of participants with HIV-1 RNA <50 c/mL was lower in the <90% adherence group than the ≥90% group but similar between the 2 treatment groups within the same adherence category (Figures 2 and 3; Table 3)
- Lower response rates observed with Snapshot analysis compared with last on-treatment analysis were driven by non-virologic Snapshot failures (Table 3)

Figure 2. Proportion of Participants With HIV-1 RNA <50 c/mL at Week 144 Using Snapshot and Last On-Treatment Viral Load, by Adherence Category

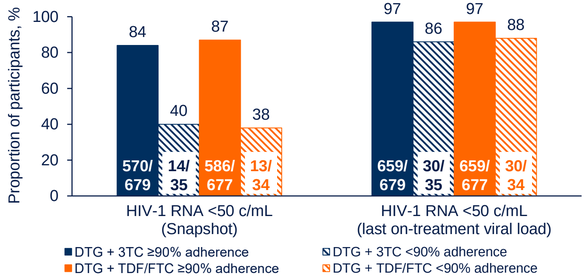
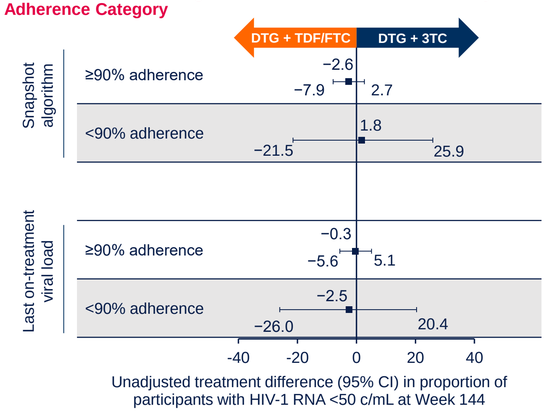


Figure 3. Treatment Differences Between Groups in Proportion of Participants Achieving HIV-1 RNA <50 c/mL at Week 144 by Adherence Category



References: 1. Altice et al. *Patient Prefer Adherence*. 2019;13:475-490. **2.** Sax et al. *Lancet*. 2017;390:2073-2082. **3.** Cahn et al. *Lancet*. 2019;393:143-155. **4.** Cahn et al. *J Acquir Immune Defic Syndr*. 2020;83:310-318. **5.** Cahn et al. *AIDS*. 2021 [Epub ahead of print]. **6.** Ait-Khaled et al. IDWeek 2020; Virtual. Poster 1024.

Table 3. Snapshot Outcomes by Adherence Category

	DTG + 3TC		DTG + TDF/FTC	
Outcomes, n (%)	≥90% (N=679)	<90% (N=35)	≥90% (N=677)	<90% (N=34)
HIV-1 RNA <50 c/mL	570 (84)	14 (40)	586 (87)	13 (38)
HIV-1 RNA ≥50 c/mL	17 (3)	6 (17)	18 (3)	3 (9)
Data in window and HIV-1 RNA ≥50 c/mL	3 (<1)	1 (3)	5 (<1)	0
Discontinued for lack of efficacy	7 (1)	3 (9)	4 (<1)	0
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	6 (<1)	1 (3)	8 (1)	3 (9)
Change in ART	1 (<1)	1 (3)	1 (<1)	0
No virologic data at Week 144	92 (14)	15 (43)	73 (11)	18 (53)
Discontinued study for AE or death	28 (4)	1 (3)	26 (4)	5 (15)
Discontinued study for other reason[a]	63 (9)	13 (37)	47 (7)	12 (35)
On study but missing data in window	1 (<1)	1 (3)	0	1 (3)

[a]Other reasons included lost to follow-up, investigator discretion, withdrawal of consent, and protocol deviations.

Discussion

- Level of adherence appeared to have a similar impact on efficacy as assessed by virologic suppression for participants in both the DTG + 3TC and DTG + TDF/FTC groups, with higher response rates in those with ≥90% adherence
- Response rates were lower using Snapshot in participants with <90% adherence, mostly driven by non-virologic reasons
- Response rates were high when last on-treatment viral load was assessed
- Limitations of this analysis include the small number of participants in the <90% adherence subgroup and the difficulty in accurately measuring adherence
- These results provide additional information on the robustness of the 2DR DTG + 3TC compared with the 3DR DTG + TDF/FTC and suggest similar regimen forgiveness and reassurance in the case of sporadic missed doses
- However, clinicians should continue to promote and support optimal adherence (ie, 'every dose, every day') for optimal virologic suppression rather than rely on a regimen's perceived forgiveness. This is essential for minimizing the risk of true virologic failure with resistance development and, importantly, reducing the risk of inflammation and of HIV transmission in people with intermittent periods of viremia

Conclusions

- In GEMINI-1 and GEMINI-2, similar proportions of participants, regardless of adherence level, achieved HIV-1 RNA <50 c/mL at Week 144 when DTG + 3TC was compared with DTG + TDF/FTC
- Fewer participants with <90% adherence (vs those with ≥90% adherence) achieved HIV-1 RNA <50 c/mL at Week 144, regardless of regimen; the effect of lower adherence on virologic response was similar between DTG + 3TC and DTG + TDF/FTC
- These results support the durability of DTG + 3TC compared with standard-of-care 3DRs through 144 weeks of treatment and suggest similar regimen forgiveness
- Clinicians should continue to promote and support optimal adherence for optimal virologic suppression

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