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

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DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhiitor class, or lamivudine

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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 (i.e. <95%)[2]
- In the GEMINI-1 (NCT02831673) and GEMINI-2 (NCT02831764) trials, the 2-drug regimen (2DR) DOVATO (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[7]

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GEMINI-1 and GEMINI-2 Study Design[7]

- 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[3]

Eligibility criteria:
- VL 1,000–500,000 copies/mL at screening
- ≤10 days of prior ART
- No major RT or PI resistance mutation
- No HBV infection or need for HCV therapy
- CrCl >50 mL/min

Primary endpoint:
Proportion of participants with HIV-1 RNA <50 copies/mL (ITT–E Snapshot)[a]

Countries:

Argentina	Australia	Belgium
Canada	France	Germany
Italy	Republic of Korea	Mexico
Netherlands	Peru	Poland
Portugal	Romania	Russian Federation
South Africa	Spain	Switzerland
Taiwan	United Kingdom	United States

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

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Methods[7]

- 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

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Demographics and Baseline Characteristics in GEMINI-1 and GEMINI-2 (ITT-E Population)[7]

- In each treatment group, 5% of participants had <90% adherence through Week 144
- For this analysis, <10% of participants were missing pill count data
- Demographics and baseline characteristics of participants in GEMINI-1 and GEMINI-2 were well balanced between treatment groups[3-5]

Demographic/Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y ≥50 y, n (%)	32 (18–72) 65 (9)	33 (18–70) 80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%) African American/African Heritage Asian White Other	 90 (13) 71 (10) 484 (68) 71 (10)	 71 (10) 72 (10) 499 (70) 75 (10)
Ethnicity, n (%) Hispanic/Latino Not Hispanic/Latino	 215 (30) 501 (70)	 232 (32) 485 (68)
HIV-1 RNA, median (range), $\log_{10}$ c/mL >100,000, n (%)	4.43 (1.59–6.27) 140 (20)	4.46 (2.11–6.37) 153 (21)
CD4+ cell count, median (range), cells/mm^3 ≤200, n (%)	427.0 (19–1,399) 63 (9)	438.0 (19–1,497) 55 (8)

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

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Adherence Results and Baseline Characteristics (ITT-E Population)[7]

- Baseline HIV-1 RNA and CD4+ cell counts were comparable across adherence categories

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 (19–1,399)	414 (25–884)
≥90%	426 (19–1,364)	442 (19–1,497)

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

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Impact of Adherence[7]

- 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
- Lower response rates observed with Snapshot analysis compared with last on-treatment analysis were driven by non-virologic Snapshot failures

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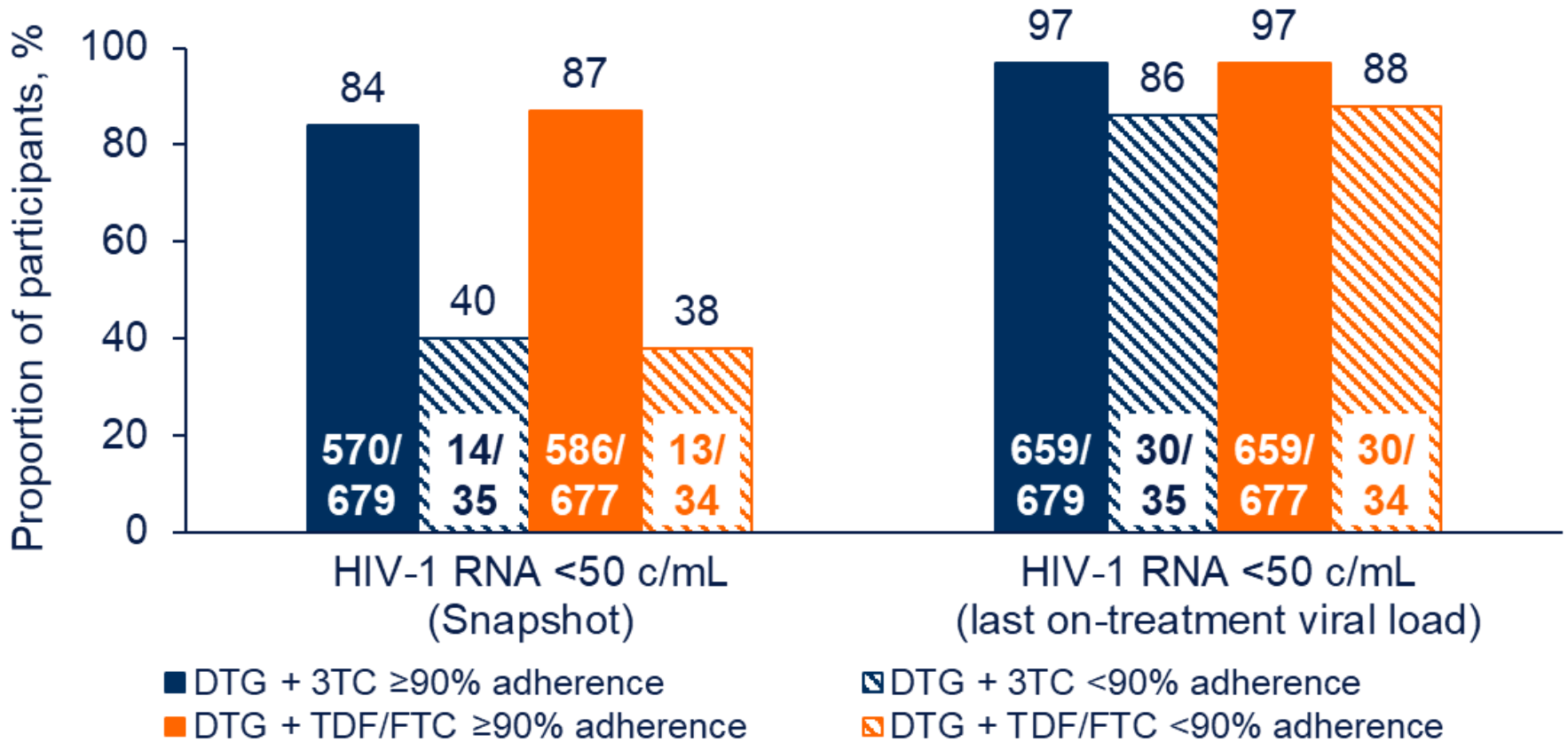
Proportion of Participants With HIV-1 RNA <50 c/mL at Week 144 Using Snapshot and Last On-Treatment Viral Load, by Adherence Category[7]



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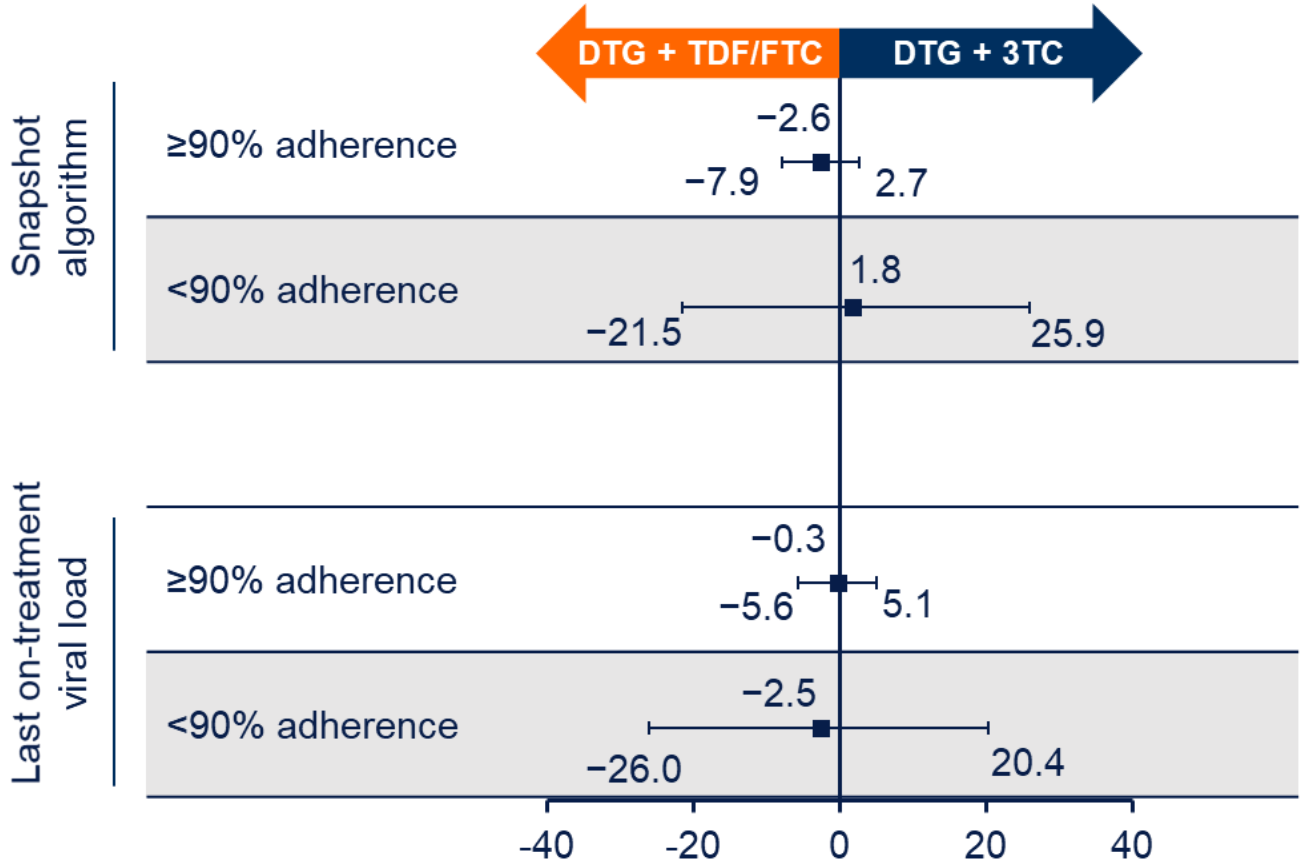
Treatment Differences Between Groups in Proportion of Participants Achieving HIV-1 RNA <50 c/mL at Week 144 by Adherence Category[7]



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Snapshot Outcomes by Adherence Category[7]

Outcomes, n (%)	DTG + 3TC		DTG + TDF/FTC	
	≥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
Discontinues 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.

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Discussion[7]

- 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 (i.e. '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

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Conclusions[7]

- 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 DOVATO (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 DOVATO and DTG + TDF/FTC
- These results support the durability of DOVATO 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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References: 1. Altice F, et al. Patient Prefer Adherence 2019;13:475–90. **2.** Sax P, et al. Lancet 2017;390:2073–82. **3.** Cahn P, et al. Lancet 2019;393:143–55. **4.** Cahn P, et al. J Acquir Immune Defic Syndr 2020;83:310–8. **5.** Cahn P, et al. AIDS 2021; doi: 10.1097/QAD.0000000000003070 [Online ahead of print]. **6.** Ait-Khaled M, et al. Virtual IDWeek 2020; Poster 1024. **7.** Fernvik E, et al. EACS 2021; Poster PE2/63.