Meta-Analysis of DTG/3TC vs DTG 3DRs in ART-Naive People With High Baseline Viral Loads and Low CD4+

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Plain Language Summary

- A meta-analysis combines data from several clinical studies to provide a better understanding of how well a treatment works overall, not just in one study
- Across 5 studies, the 2-drug regimen (2DR) dolutegravir/lamivudine (DTG/3TC) kept HIV under control as well as DTG 3-drug regimens (3DRs), with no new safety concerns, even in people who started treatment with high virus levels or low immune cell counts

Introduction

- DTG/3TC is globally approved for use regardless of viral load (VL) in individuals naive to antiretroviral therapy (ART)
- Global treatment guidelines have adopted a cautious approach for use in individuals with very high VL despite lack of restriction in product labeling
- Notably, the percentage of participants with baseline (BL) HIV-1 RNA ≥500,000 c/mL in the phase 3 GEMINI-1/-2 studies is comparable to those in registrational trials for other recommended first-line regimens
- Multiple post-approval clinical studies demonstrated similar efficacy and safety outcomes between DTG/3TC and comparators for people with HIV-1 across a wide spectrum of BL HIV-1 RNA levels
- **Objective:** A meta-analysis was conducted across 5 ViiV-sponsored and investigator-initiated clinical trials to compare efficacy, confirmed virologic withdrawal (CVW) rates, and tolerability among participants with very high BL VL (≥500,000 c/mL) and/or low CD4+ cell count (<200 cells/mm^3) receiving DTG/3TC or dolutegravir + tenofovir disoproxil fumarate/lamivudine or emtricitabine (DTG + TDF/XTC) through Week 48

Methods

- Data from participants naive to ART who received DTG/3TC or DTG + TDF/XTC from the GEMINI-1/-2, STAT, D2ARLING, and DOLCE studies were analyzed through Week 48
- Primary endpoint was the proportion with HIV-1 RNA <50 c/mL at Week 48 in each treatment group (2DR and 3DR) per US Food and Drug Administration (FDA) Snapshot algorithm by BL HIV-1 RNA and CD4+ cell count category
- Secondary endpoints included
  - Rate of CVW by Week 48 and resistance development
  - Drug-related adverse events (AEs)
  - AE-related treatment withdrawals
- A Bayesian hierarchical logistic-regression model with g-computation was used to analyze data. The probability of virologic suppression was estimated by treatment while adjusting for study design differences; BL VL and CD4+ cell count were incorporated as continuous variables, avoiding arbitrary cutoffs
- Average risk difference (3DR-2DR) in virologic suppression between treatments was calculated, with 95% credible interval (CrIs) generated. Density weighting was applied to weight each BL value according to how frequently it appeared in the pooled population before producing treatment estimates

Table 1. Baseline Demographics and Characteristics: Overall Meta-Analysis Population

	DTG/3TC (GEMINI-1, GEMINI-2, STAT, DOLCE, D2ARLING) (n=1036)	DTG + TDF/XTC (GEMINI-1, GEMINI-2, DOLCE, D2ARLING) (n=825)	Total population (n=1861)
Median (range) age, y[a]	32.5 (18-72)	34.0 (18-70)	33.0 (18-72)
≥50 y, n (%)	124 (12)	99 (12)	223 (12)
Female, n (%)[b]	180 (17)	143 (17)	323 (17)
Black race, n (%)	171 (17)	79 (10)	250 (13)
Median (range) plasma HIV-1 RNA, c/mL	38,017 (39-68,706,840)	33,681 (213-3,589,622)	35,608 (39-68,706,840)
<500,000 c/mL, n (%)	960 (93)	786 (95)	1746 (94)
≥500,000 c/mL, n (%)	75 (7)	39 (5)	114 (6)
500,000-1,000,000 c/mL, n (%)	43 (4)	29 (4)	72 (4)
≥1,000,000 c/mL, n (%)	32 (3)	10 (1)	42 (2)
Median (range) CD4+ cell count, cells/mm^3	376 (1-1466)	395 (3-1497)	387 (1-1497)
<100 cells/mm^3, n (%)	103 (10)	55 (7)	158 (8)
100-<200 cells/mm^3, n (%)	135 (13)	75 (9)	210 (11)
200-<350 cells/mm^3, n (%)	233 (22)	207 (25)	440 (24)
≥350 cells/mm^3, n (%)	564 (54)	485 (59)	1049 (56)

Note: In GEMINI-1/-2 and D2ARLING, DTG and 3TC were administered as separate tablets. [a]Excluding participants from DOLCE and D2ARLING (exact ages not available; only data for those aged ≥50 years are shown). [b]Assigned female sex at birth.

- Overall, 12% were aged ≥50 years, 17% were assigned female sex at birth, 13% were Black, 114 participants had BL VL ≥500,000 c/mL, and 368 participants had BL CD4+ cell count <200 cells/mm^3 (Table 1)

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References: 1. Cahn et al. *AIDS*. 2022;36:39-48. **2.** Fraysse et al. *Infect Dis Ther*. 2025;14:357-383.

DTG/3TC demonstrates virologic efficacy, safety, and resistance outcomes comparable to DTG-based triple therapy across the entire baseline VL and CD4+ cell count spectrum, including very high VL (≥500,000 c/mL) and very low CD4+ cell count, providing robust evidence to remove VL-based cautions for its use among individuals naive to ART from treatment guidelines

Table 2. Baseline Demographics and Characteristics: High VL and Low CD4+ Cell Count Sub-Population

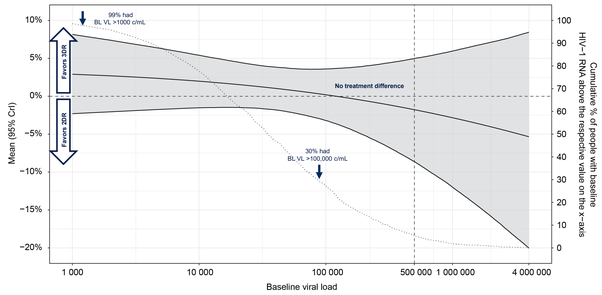
	DTG/3TC (n=1036)				DTG + TDF/XTC (n=825)			
	VL <500,000 (n=960)	VL ≥500,000 (n=75)	CD4+ <200 (n=238)	CD4+ ≥200 (n=797)	VL <500,000 (n=786)	VL ≥500,000 (n=39)	CD4+ <200 (n=130)	CD4+ ≥200 (n=692)
Age, median (range), y	32.0 (18-71)	37.0 (22-72)	38.0 (18-72)	32.0 (18-69)	33.0 (18-70)	38.0 (22-58)	34.5 (20-70)	33.0 (18-66)
Female, n (%)[a]	167 (17)	13 (17)	52 (22)	128 (16)	137 (17)	6 (15)	33 (25)	108 (16)
Black race, n (%)	153 (16)	17 (23)	47 (20)	124 (16)	72 (9)	7 (18)	21 (16)	57 (8)
BL CD4+ cell count <200 cells/mm^3, %	19	68	NA	NA	14	56	NA	NA
BL VL ≥500,000 c/mL, %	NA	NA	21	3	NA	NA	17	2

[a]Assigned female sex at birth.

- BL characteristics were generally similar between treatments among BL VL and CD4+ cell count subgroups, apart from approximately twice as many participants with BL VL ≥500,000 c/mL in the DTG/3TC (n=75) vs DTG + TDF/XTC (n=39) group (Table 2)
- In those with BL VL ≥500,000 c/mL, 68% in the DTG/3TC vs 56% in the DTG + TDF/XTC group also had BL CD4+ cell count <200 cells/mm^3. In those with BL CD4+ cell count <200 cells/mm^3, 21% in the DTG/3TC vs 17% in the DTG + TDF/XTC group also had BL VL ≥500,000 c/mL (Table 2)

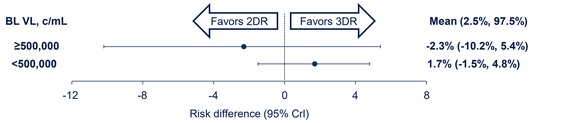
Results

Figure 1. Mean Risk Difference in Virologic Suppression Rates Between Treatments at Week 48 Across the Baseline VL Spectrum



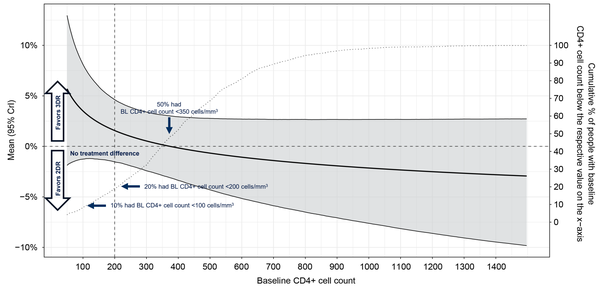
- Figure 1 shows the treatment difference in virologic suppression rates at any given BL VL. Differences are adjusted for actual CD4+ cell counts and other BL characteristics at that VL level to reflect estimates for people with similar underlying profiles
- Overall, the mean risk difference varied modestly (generally within 2.5%) across the entire BL VL range. There was no statistical difference in virologic suppression rates at any BL VL level (ie, the 95% CrI band consistently included zero)
- Among those with BL VL ≥500,000 c/mL, the estimates continued to include zero, indicating no meaningful reduction of DTG/3TC efficacy even at very high VLs

Figure 2. Adjusted Treatment Risk Difference (3DR-2DR) in Proportion Achieving HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot Algorithm) by Baseline VL Category



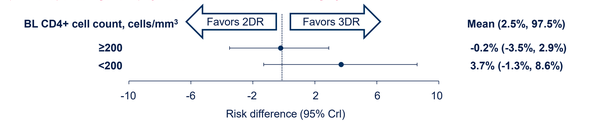
- In Figure 2, the risk difference remains close to zero, and the CrI includes zero, indicating comparable efficacy across the VL spectrum, including ≥500,000 c/mL
- For participants with BL VL ≥500,000 c/mL, adjusted Week 48 virologic suppression rates were 86.7% for DTG/3TC vs 84.4% for DTG + TDF/XTC, with a risk difference of -2.3% (95% CrI, -10.2%, 5.4%), indicating no meaningful treatment difference
- Similarly, there was no statistical difference in virologic response rates or treatment differences for participants with BL VL <500,000 c/mL

Figure 3. Mean Risk Difference in Virologic Suppression Rates Between Treatments at Week 48 Across the Baseline CD4+ Cell Spectrum



- Similarly, across the CD4+ cell range, the mean risk difference was generally within 3%, and the 95% CrI band consistently included zero, indicating no meaningful treatment difference at any BL CD4+ cell count level
- Among participants with CD4+ cell count <200 or <100 cells/mm^3, risk difference estimates continued to include zero, indicating high and comparable efficacy between treatments even with low BL CD4+ cell count

Figure 4. Adjusted Treatment Risk Difference (3DR-2DR) in Proportion Achieving HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot Algorithm) by Baseline CD4+ Cell Count Category



- For participants with BL CD4+ cell count <200 cells/mm^3, adjusted Week 48 virologic suppression rates were 86.3% for DTG/3TC vs 90.1% for DTG + TDF/XTC, with a risk difference of 3.7% (95% CrI, -1.3%, 8.6%), indicating no meaningful treatment difference
- Similarly, there was no statistical difference in virologic response rates or treatment differences for participants with BL CD4+ cell count <100 or ≥350 cells/mm^3

Table 3. Proportion With CVW by Week 48 by Baseline VL and CD4+ Cell Count

	2DR DTG/3TC Mean (95% CrI)	3DR DTG + TDF/XTC Mean (95% CrI)	3DR-2DR treatment difference Mean (95% CrI)
BL VL			
<500,000 c/mL	0.5 (0.1, 1.2)	0.2 (0.0, 0.7)	-0.3 (-1.0, 0.3)
≥500,000 c/mL	1.7 (0.4, 4.6)	1.4 (0.1, 5.3)	-0.3 (-3.6, 3.9)
BL CD4+ cell count			
<200 cells/mm^3	1.3 (0.4, 3.0)	0.5 (0.0, 1.8)	-0.9 (-2.6, 0.6)
≥200 cells/mm^3	0.6 (0.2, 1.2)	0.4 (0.1, 1.0)	-0.2 (-0.9, 0.6)

- CVW rates were low and comparable between treatments, with no statistical differences between treatments or by BL VL or CD4+ cell count subgroups
- No resistance occurred through Week 48 in any study as previously reported

Table 4. Summary of AE Profile

	DTG/3TC (n=1036)	DTG + TDF/XTC (n=825)
Any AE, n (%)	746 (72)	611 (74)
Drug related	134 (13)	160 (19)
AE leading to withdrawal, n (%)	20 (2)	16 (2)
Drug related	7 (<1)	10 (1)
Any grade ≥3 AE, n (%)	65 (6)	54 (7)
Drug related	7 (<1)	7 (<1)
Any serious AE, n (%)	62 (6)	52 (6)
Drug related	3 (<1)	3 (<1)

- Drug-related AEs were more common in the DTG 3DR (19%) than the DTG/3TC group (13%)
- Drug-related grade ≥3 AEs were infrequent and consistent with the known safety profile of DTG/3TC[1]
- Few participants discontinued treatment because of AEs
- Overall, both DTG/3TC and DTG-based 3DRs were well tolerated through 48 weeks

Discussion

- This is the first efficacy meta-analysis between DTG/3TC vs DTG 3DRs that accounts for BL VL and CD4+ cell count for each participant to establish virologic suppression rates across the VL and CD4+ cell count spectrum
- Analysis strengths are inclusion of randomized comparative trial data and methods that avoid use of arbitrary VL/CD4+ cell count subgroups to provide more reliable and clinically meaningful estimates across the full BL-risk range
- This analysis of clinical trial data supports real-world findings from Fraysse et al,[2] which demonstrated DTG/3TC had 97% effectiveness through Week 48 in 215 diverse individuals naive to ART with BL VL ≥100,000 c/mL across 10 real-world cohorts
- Limitations of this present analysis include limited representation of data at extreme BL values, lack of generalizability to non-studied populations, and absence of long-term outcomes beyond Week 48 due to study design limitations

Conclusions

- **DTG/3TC performed comparably to DTG-based 3DRs across all BL VLs, including very high VL (≥500,000 c/mL)**
  - Among participants with BL VL ≥500,000 c/mL, Week 48 suppression rates were 86.7% for DTG/3TC vs 84.4% for 3DR (risk difference, -2.3% [95% CrI, -10.2%, 5.4%])
  - Across the entire range of VLs for participants in this analysis, the risk difference remained low, and CrIs consistently included zero, indicating no meaningful difference
  - Although smaller, the VL ≥500,000 c/mL subgroup in this data set is more than double the high VL cases initially evaluated by the FDA and global regulatory authorities for single-tablet regimen approvals (including Dovato and Biktarvy), providing a substantially stronger evidence base than prior registrational trials
- **DTG/3TC remains robust in people across all BL CD4+ cell counts, including low and very low CD4+ cell count**
  - Among participants with CD4+ cell count <200 cells/mm^3, Week 48 virologic suppression rates were 86.3% for DTG/3TC vs 90.1% for 3DR (risk difference, 3.7% [95% CrI, -1.3%, 8.6%])
- CVW was infrequent, similar between groups, and did not differ by BL VL or CD4+ cell count category. Zero resistance was reported through Week 48. There was no difference in safety or tolerability profiles
- **This meta-analysis integrates robust randomized controlled trial evidence, which is concordant with real-world results, offering a substantially stronger foundation than prior subgroup analyses, confirming high DTG/3TC efficacy, even at very high VL and very low CD4+ cell count. These data support removal of any VL-based guideline cautions for DTG/3TC**

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