Comparable Efficacy of Dolutegravir/Lamivudine Versus Second-Generation Integrase Strand Transfer Inhibitor–Based 3-Drug Regimens Across the Baseline Viral Load Continuum: A Participant-Level Meta-Analysis

P053

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Key Takeaways

- DTG/3TC demonstrated efficacy comparable to second-generation integrase strand transfer inhibitor–based 3DRs across the studied baseline VL and CD4+ cell count continuums through Week 48
- Among participants with baseline VL ≥500,000 c/mL, virologic suppression rates were high, with a 99.8% probability of non-inferiority (10% non-inferiority margin) for DTG/3TC vs DTG- and BIC-based 3DRs
- Rates of CVW were low, no treatment-emergent resistance was observed, and overall safety outcomes were comparable between treatment groups
- These findings support the use of DTG/3TC in people initiating treatment with high or very high baseline VLs

Plain Language Summary

- Dolutegravir/Lamivudine is a 2-drug HIV treatment that can be used by people starting treatment regardless of the amount of virus in their blood
- We combined data from 6 clinical trials to compare dolutegravir/lamivudine with 3-drug HIV treatments, including among people who started treatment with very high virus levels
- Dolutegravir/Lamivudine controlled HIV as well as 3-drug medicines through 48 weeks in people who began treatment with very high virus levels in their blood; no resistance to treatment was observed

Introduction

- The 2-drug regimen dolutegravir/lamivudine (DTG/3TC) is approved for HIV treatment in people naive to antiretroviral therapy (ART) regardless of baseline viral load (VL) and in people with virologic suppression switching from a stable ART regimen[1,2]
- DTG/3TC has demonstrated durable efficacy across a broad range of baseline VLs and CD4+ cell counts, including in individuals with very high VLs (≥500,000 c/mL) and advanced disease[3-5]
- In the US Department of Health and Human Services' "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV," DTG/3TC is now recommended irrespective of baseline VL, reflecting the growing evidence supporting its use across baseline risk groups[6]
- Individuals with very high baseline VLs remain relatively underrepresented in clinical trials, contributing to greater uncertainty around treatment-effect estimates in this population[6,7]
- We conducted a participant-level Bayesian meta-analysis of 6 clinical studies across various clinical settings, including data from the randomized head-to-head VOGUE study comparing DTG/3TC with the 3-drug regimen (3DR) bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF), to evaluate Week 48 efficacy, resistance, and safety outcomes across the baseline VL and CD4+ cell count continuum

Methods

Research Design

- Participant-level data from 6 studies (N=2314) evaluating DTG/3TC among adults naive to ART were pooled, representing diverse clinical settings, including rapid-start care, advanced HIV disease, treatment initiation without baseline resistance results, and contemporary DTG- and BIC-based comparisons (Table 1)

Table 1. Summary of Studies of DTG/3TC in ART-Naive Populations Included in the Meta-Analysis[a]

Study	Clinical setting	Comparator
GEMINI-1/-2[8,b]	Pivotal studies supporting regulatory approval in ART-naive population	DTG + TDF/FTC
STAT[9,c]	Rapid-start (test-and-treat) initiation before availability of BL laboratory results	None
DOLCE[5,d]	Advanced HIV disease (CD4+ cell count ≤200 cells/mm^3)	DTG + TDF/XTC
D2ARLING[10,d]	Treatment initiation without availability of BL genotypic resistance testing results	DTG + TDF/XTC
VOGUE[11,e]	Head-to-head comparison using a test-and-treat approach with no baseline VL or CD4+ cell count restriction	BIC/FTC/TAF

BL, baseline; TDF, tenofovir disoproxil fumarate; XTC, FTC or 3TC. [a]DTG and 3TC were administered as separate tablets in GEMINI-1/-2 and D2ARLING and as a single tablet in STAT, DOLCE, and VOGUE. [b]Phase 3, double-blind, randomized studies. [c]Phase 3b, single-arm study. [d]Phase 4, open-label, randomized study. [e]Phase 3b, open-label, randomized study.

- The primary endpoint was the proportion of individuals with HIV-1 RNA <50 c/mL at Week 48, per the US Food and Drug Administration Snapshot algorithm, evaluated according to the baseline VL and CD4+ cell count category
- Secondary endpoints included the proportion of individuals with HIV-1 RNA <200 c/mL at Week 48 by baseline VL, rates of confirmed virologic withdrawal (CVW) and development of treatment-emergent resistance, drug-related adverse events (AEs), and AE-related treatment withdrawals

Statistical Analysis

- A participant-level Bayesian hierarchical logistic-regression model with G-computation estimated treatment effects while accounting for study-level heterogeneity and participant-level baseline characteristics
- Baseline VL and CD4+ cell count were modeled continuously, avoiding information loss from arbitrary subgroup cutoffs
- Mean risk differences in virologic suppression between treatments (DTG- or BIC-based 3DR−DTG/3TC; negative values favor DTG/3TC, positive values favor 3DR) were calculated, with 95% credible intervals (CrIs) generated
- Exploratory Bayesian posterior probabilities of non-inferiority were estimated by baseline VL and CD4+ cell count category using a 10% non-inferiority margin

Results

Baseline Demographics and Characteristics

- The pooled meta-analysis included 2314 individuals, including 192 (8%) with baseline VL ≥500,000 c/mL (Table 2)

Table 2. Baseline Demographics and Characteristics: Overall Meta-Analysis Population

Baseline parameter, median (range) or n (%)	DTG/3TC (n=1259)	DTG- or BIC-based 3DR (n=1055)	Total (N=2314)
Age, y[a]	29.0 (18-73)	30.0 (18-84)	NA
≥50	158 (13)	142 (13)	300 (13)
Assigned female sex at birth	215 (17)	178 (17)	393 (17)
African American or of African heritage	186 (15)	93 (9)	279 (12)
Ethnicity, Hispanic or Latino	453 (36)	430 (41)	883 (38)
VL, c/mL[b]	46,832 (13-68,706,840)	40,588 (13-6,000,001)	NA
<500,000	1142 (91)	979 (93)	2121 (92)
≥500,000	116 (9)	76 (7)	192 (8)
500,000-<1,000,000	62 (5)	45 (4)	107 (5)
≥1,000,000	54 (4)	31 (3)	85 (4)
CD4+ cell count, cells/mm^3[,c]	376 (1-1466)	390 (3-1497)	NA
<200	272 (22)	168 (16)	440 (19)
≥200	986 (78)	884 (84)	1870 (81)

NA, not available. [a]Excluding participants from DOLCE and D2ARLING (exact ages not available; only data for those aged ≥50 years are shown). [b]Baseline VL was missing for 1 participant in the DTG/3TC group. [c]Baseline CD4+ cell count was missing for 1 participant in the DTG/3TC group and 3 participants in the 3DR group.

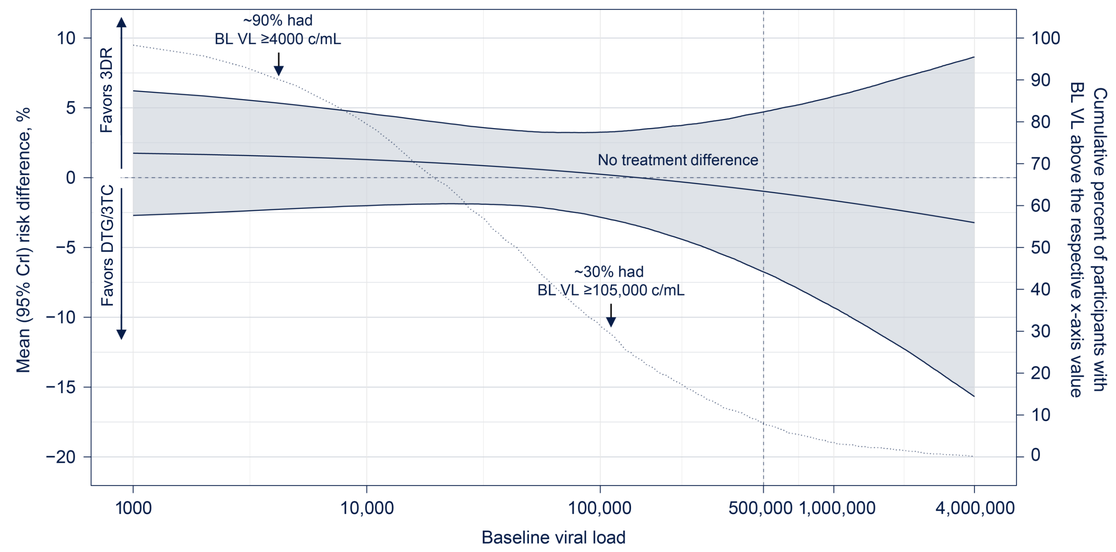
Baseline Disease Characteristics Among Population With Very High VL or Low CD4+ Cell Count

- Among individuals with baseline VL ≥500,000 c/mL:
  - 58% (67/116; DTG/3TC) and 47% (36/76; 3DR) also had baseline CD4+ cell count <200 cells/mm^3
- Among individuals with baseline CD4+ cell count <200 cells/mm^3:
  - 25% (67/272; DTG/3TC) and 21% (36/168; 3DR) also had baseline VL ≥500,000 c/mL

Comparable Week 48 Efficacy Across the Baseline VL and CD4+ Cell Count Continuum

- Virologic suppression remained high for both DTG/3TC and second-generation integrase strand transfer inhibitor–based 3DRs across the studied baseline VL range
- Across the baseline HIV-1 RNA continuum, the adjusted mean risk difference (3DR−DTG/3TC) in Week 48 virologic suppression (HIV-1 RNA <50 c/mL) between DTG/3TC and DTG- or BIC-based 3DRs ranged from 1.3% (95% CrI, -2.0%, 4.6%) to -1.6% (95% CrI, -9.3%, 5.8%), with 95% CrIs including zero across the evaluated continuum (Figure 1)
- Across the baseline CD4+ cell count continuum, the adjusted mean risk difference (3DR−DTG/3TC) in Week 48 virologic suppression (HIV-1 RNA <50 c/mL) between DTG/3TC and DTG- or BIC-based 3DRs ranged from 0.6% (95% CrI, -4.1%, 5.2%) to -0.1% (95% CrI, -5.3%, 4.7%), with 95% CrIs including zero across the evaluated continuum

Figure 1. Mean Risk Difference in Week 48 Virologic Suppression (DTG- or BIC-Based 3DR−DTG/3TC) Across the Baseline VL Continuum

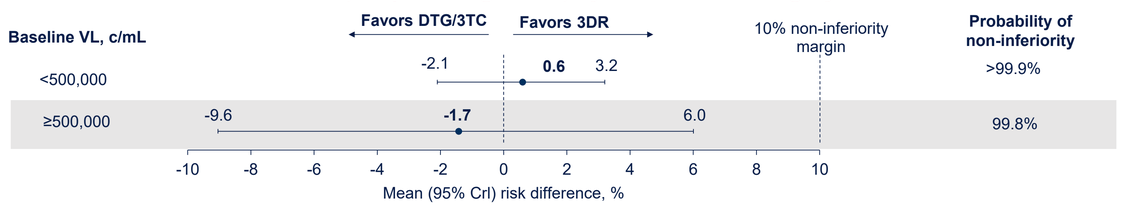


Differences are adjusted for actual CD4+ cell counts and other baseline characteristics at that VL level to reflect estimates for individuals with similar underlying profiles. BL, baseline.

Comparable Efficacy Was Maintained at Very High Baseline VLs

- In the very high baseline VL subgroup, estimated adjusted mean Week 48 virologic suppression was comparable between DTG/3TC and 3DRs, with a 99.8% probability of non-inferiority using a 10% non-inferiority margin (Figure 2)
  - HIV-1 RNA <50 c/mL: 83.3% for DTG/3TC vs 81.6% for 3DR (mean virologic suppression risk difference [3DR−DTG/3TC], -1.7%; 95% CrI, -9.6%, 6.0%)
  - HIV-1 RNA <200 c/mL: 92.7% for DTG/3TC vs 88.6% for 3DR (mean virologic suppression risk difference [3DR−DTG/3TC], -4.1%; 95% CrI, -10.3%, 1.3%)

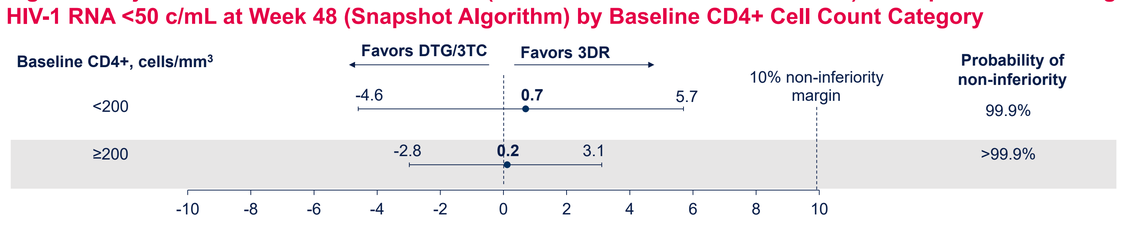
Figure 2. Adjusted Treatment Risk Difference (DTG- or BIC-Based 3DR−DTG/3TC) in Proportion Achieving HIV-1 RNA <50 c/mL at Week 48 (Snapshot Algorithm) by Baseline VL Category



Comparable Efficacy Was Maintained at Low Baseline CD4+ Cell Count

- In the low baseline CD4+ cell count subgroup, estimated adjusted mean Week 48 virologic suppression was comparable between DTG/3TC and 3DRs, with a 99.9% probability of non-inferiority using a 10% non-inferiority margin (Figure 3)
  - HIV-1 RNA <50 c/mL: 86.1% for DTG/3TC vs 86.7% for 3DR (mean virologic suppression risk difference [3DR−DTG/3TC], 0.7%; 95% CrI, -4.6%, 5.7%)

Figure 3. Adjusted Treatment Risk Difference (DTG- or BIC-based 3DR−DTG/3TC) in Proportion Achieving HIV-1 RNA <50 c/mL at Week 48 (Snapshot Algorithm) by Baseline CD4+ Cell Count Category



CVW Was Low Across Subgroups With No Treatment-Emergent Resistance Through Week 48

- CVW rates were low and comparable between treatments, with treatment effect estimates remaining small and corresponding to 95% CrIs including zero:
  - CVW rates for baseline VL ≥500,000 c/mL: 2.4% for DTG/3TC vs 2.0% for 3DR (mean CVW risk difference, -0.4%; 95% CrI, -4.0%, 3.2%)
  - CVW rates for baseline CD4+ cell count <200 cells/mm^3: 1.8% for DTG/3TC vs 1.5% for 3DR (mean CVW risk difference, -0.3%; 95% CrI, -2.4%, 2.0%)
- No treatment-emergent resistance was observed in any group through Week 48

Comparable Safety Through Week 48

- Drug-related AEs occurred less frequently with DTG/3TC than with 3DRs (13% vs 19%; Table 3)
- Serious AEs, grade ≥3 AEs, and discontinuation-related AEs were uncommon in both groups

Table 3. Summary of Week 48 AE Profile

AE, n (%)	DTG/3TC (n=1259)	DTG- or BIC-based 3DR (n=1055)
Any AE	932 (74)	817 (77)
Drug related	158 (13)	198 (19)
AE leading to withdrawal	22 (2)	19 (2)
Drug related	7 (<1)	12 (1)
Any grade ≥3 AE	81 (6)	68 (6)
Drug related	7 (<1)	8 (<1)
Any serious AE	78 (6)	64 (6)
Drug related	3 (<1)	3 (<1)

Conclusions

- DTG/3TC demonstrated comparable Week 48 efficacy to DTG- and BIC-based 3DRs across the studied baseline VL and CD4+ cell count continuums, including among people with baseline VL ≥500,000 c/mL
- High efficacy was maintained among individuals with baseline VL ≥500,000 c/mL and among those with baseline CD4+ cell count <200 cells/mm^3, with ≥99.8% probability of non-inferiority
- CVW rates remained low, no treatment-emergent resistance was observed through Week 48, and safety findings were consistent with the established profiles of DTG/3TC and 3DRs

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