EP0172

Efficacy of dolutegravir plus lamivudine in treatment-naïve people with HIV with baseline transmitted drug-resistance mutations: a subanalysis of the D2ARLING study

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Funded by: ViiV Healthcare

Key takeaway

DTG/3TC showed high efficacy, comparable to 3-drug regimens, even in the presence of **transmitted resistance mutations.**

Introduction

The two-drug regimen DTG+3TC is a recommended treatment option for antiretroviral-naïve people with HIV (PWH). In the pivotal GEMINI 1-2 trials, participants with any detectable transmitted resistance-associated mutations (tRAMs) were excluded regardless of their impact on the regimen. Consequently, the potential effect of tRAMs that do not compromise the activity of DTG+3TC regimen on virological response has not been assessed in randomized clinical trials. This preplanned subanalysis of the D2ARLING study aimed to evaluate the efficacy of DTG+3TC compared to DTG+TDF/XTC in the context of such tRAMs.

Methods

This is a preplanned subanalysis of the D2ARLING trial, a randomized, open-label, phase IV study that evaluated DTG+3TC versus DTG+TDF/XTC in treatment-naïve PWH without baseline resistance testing information (figure 1).[1] Baseline genotypic resistance testing (RT and PI genes) was performed but remained blinded until study completion. This subanalysis included participants with baseline resistance results. Efficacy was assessed as the proportion of participants achieving HIV-1 RNA <50 copies/mL at week 48 in the presence of major NRTI, NNRTI, or PI tRAMs (IAS-USA mutation list, 2023) (INSTI-tRAMs were not tested). Analyses were conducted using the ITT-exposed snapshot algorithm, and an observed analysis (participants with available HIV-1 RNA data and those who discontinued due to lack of efficacy) (ClinicalTrials.gov: NCT04549467).

Results

Of the 214 participants enrolled in the primary study, three were excluded from this sub analysis due to amplification failure of the resistance test. The remaining 211 participants were included in the analysis: 104 received DTG+3TC and 107 received DTG+TDF/XTC.

Major tRAMs were detected in 24.6% of participants, with no significant differences between treatment arms: 26.9% (28/104) in the DTG+3TC group and 22.4% (24/107) in the DTG+TDF/XTC group (p = 0.52). Overall, the distribution of participants with tRAMs by drug class was as follows: NNRTIs 21.3%, PIs 2.8%, and NRTIs 0.5%, with no significant differences between treatment arms. Two NRTI tRAMs (M41L/V75I) were detected in a single participant receiving DTG+3TC, neither of which compromised susceptibility to 3TC (table 1).

Overall, participants with tRAMs had lower baseline HIV-1 RNA (27,520 copies/mL [IQR: 8,253–64,137] vs. 49,600 [IQR: 14,900–149,000], p=0.014).

At week 48, among participants with tRAMs, 86% in the DTG+3TC group (24/28) and 92% in the DTG+TDF/XTC group (22/24) achieved HIV-1 RNA <50 copies/mL (p=0.67) (ITT-exposed analysis). In the observed analysis, 96% in the DTG+3TC group (24/25) and 96% in the DTG+TDF/XTC group (22/23) achieved suppression (p=1). Within the DTG+3TC group, suppression rates were comparable regardless of the presence or absence of tRAMs (96% vs. 99%, p=0.45) (observed analysis) (figure 2).

Among participants with tRAMs, no protocol-defined virological failures occurred in the DTG+3TC group, while one was reported in the DTG+TDF/XTC group. Genotypic resistance testing performed during the failure did not amplify. Immunological response, measured as the change in CD4+ T-cell count from baseline to week 48 (observed analysis), was also similar between treatment arms among participants with tRAMs. Median CD4+ count increased by 225 cells/µL in the DTG+3TC group and by 195 cells/µL in the DTG+TDF/XTC group (p = 0.364).

1. Cordova E, Hernandez Rendon J, Mingrone V, et al. Lancet HIV. 2025;12:e95-e104

Figure 1. D2ARLING study design

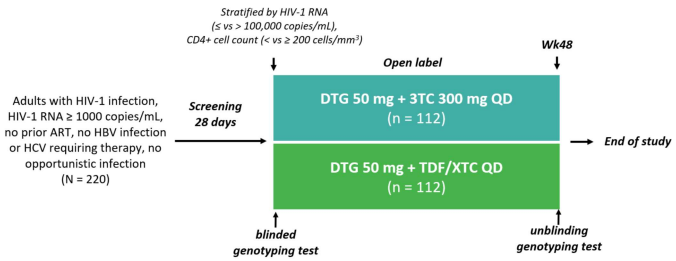
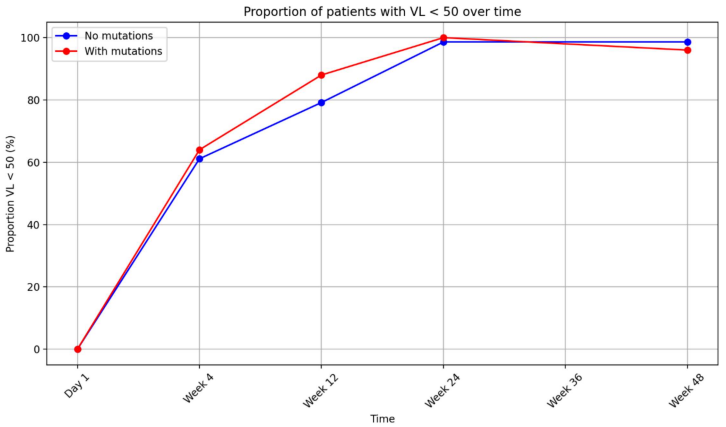


Table 1. Distribution of major mutations in baseline blinded genotyping resistance tests by each treatment group

Mutation	Total (N=211)	DTG-3TC (N=104)	DTG-TDF/XTC (N=107)	p value
Participants with ≥1 RAMs^	**52 (24.6%)**	**28 (26.9%)**	**24 (22.4%)**	**0.52**
Participants with ≥1 NRTI-RAMs^	**1 (0.5%)**	**1 (1.0%)**	**0 (0.0%)**	**0.493**
M41L	1 (0.5%)	1 (1.0%)	0 (0.0%)	0.309
V75I	1 (0.5%)	1 (1.0%)	0 (0.0%)	0.309
Participants with ≥1 NNRTI-RAMs^	**45 (21.3%)**	**25 (24.0%)**	**20 (18.7%)**	**0,402**
K101E	3 (1.4%)	1 (1.0%)	2 (1.9%)	0.578
K103N	21 (10.0%)	13 (12.5%)	8 (7.5%)	0.223
K103S	8 (3.8%)	3 (2.9%)	5 (4.7%)	0.497
V106A	1 (0.5%)	0 (0.0%)	1 (0.9%)	0.323
V106M	1 (0.5%)	0 (0.0%)	1 (0.9%)	0.323
V108I	1 (0.5%)	1 (1.0%)	0 (0.0%)	0.309
E138A	11 (5.2%)	7 (6.7%)	4 (3.7%)	0.328
E138G	2 (0.9%)	0 (0.0%)	2 (1.9%)	0.161
Y181C	3 (1.4%)	3 (2.9%)	0 (0.0%)	0.077
Y188L	2 (0.9%)	2 (1.9%)	0 (0.0%)	0.149
G190A	3 (1.4%)	2 (1.9%)	1 (0.9%)	0.544
G190S	2 (0.9%)	1 (1.0%)	1 (0.9%)	0.984
H221Y	6 (2.8%)	5 (4.8%)	1 (0.9%)	0.091
P225H	2 (0.9%)	2 (1.9%)	0 (0.0%)	0.149
Participants with ≥ 1 PI-RAMs^	**6 (2.8%)**	**2 (1.9%)**	**4 (3.7%)**	**0,683**
M46I	1 (0.5%)	0 (0.0%)	1 (0.9%)	0.323
I54V	1 (0.5%)	0 (0.0%)	1 (0.9%)	0.323
Q58E	5 (2.4%)	2 (1.9%)	3 (2.8%)	0.674
T74P	1 (0.5%)	0 (0.0%)	1 (0.9%)	0.323
N88S	1 (0.5%)	0 (0.0%)	1 (0.9%)	0.323

DTG-3TC= dolutegravir and lamivudine. DTG-TDF/XTC= dolutegravir, tenofovir disoproxil fumarate and, emtricitabine or lamivudine. *All baseline genotypic drug-resistance testing was unblinded upon completion of the study. ^Major mutations according to the IAS-USA mutations list 2023.

Figure 2. Proportion of participants with HIV-1 RNA <50 copies/mL over time stratified by presence of transmitted resistance-associated mutations within the DTG+3TC treatment group,



Conclusions

DTG/3TC showed high efficacy at week 48, comparable to DTG+TDF/XTC in participants with tRAMs not affecting this regimen. The presence of such tRAMs did not compromise treatment outcomes in treatment-naïve individuals in this setting.

Financial support: this reasearch was funded by ViiV Healthcare

Presented at IAS 2025

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