# DTG vs LPV/r (DAWNING): Efficacy by Baseline NRTI Resistance and Second-Line NRTI Use

P055

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## Introduction

- The DAWNING study[1] was conducted to evaluate the efficacy and safety of dolutegravir (DTG) + 2 nucleoside reverse transcriptase inhibitors (NRTIs) vs a current World Health Organization (WHO)[2] recommended regimen of ritonavir-boosted lopinavir (LPV/r) + 2 NRTIs in HIV-1-infected persons failing first-line therapy of a non-NRTI (NNRTI) + 2 NRTIs (ClinicalTrials.gov: NCT02227238)
  - DTG + 2 NRTIs was shown to be superior in the proportion of participants achieving viral suppression (plasma HIV-1 RNA <50 c/mL) at Week 48 compared with LPV/r + 2 NRTIs[1]
- NRTI resistance is common following virologic failure on historic first-line regimens in resource-limited settings (especially M184V/I and K65R)
  - Recycling of lamivudine (3TC) or emtricitabine (FTC) is recommended in NRTI sequencing algorithms
- The current post hoc analysis examined efficacy outcomes for different NRTI combinations in the presence of existing NRTI resistance, including when 3TC or FTC was used in the presence of M184V/I

## Methods

- Participants were randomized (1:1, stratified by Screening HIV-1 RNA and number of fully active NRTIs) to 52 weeks of open-label treatment with DTG or LPV/r + 2 investigator-selected NRTIs, including ≥1 fully active NRTI based on Screening resistance testing
- The primary endpoint was the proportion of participants with HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm)
- Post-hoc efficacy analyses were performed based on baseline NRTI resistance profile and NRTI use in the second-line background regimen

## Results

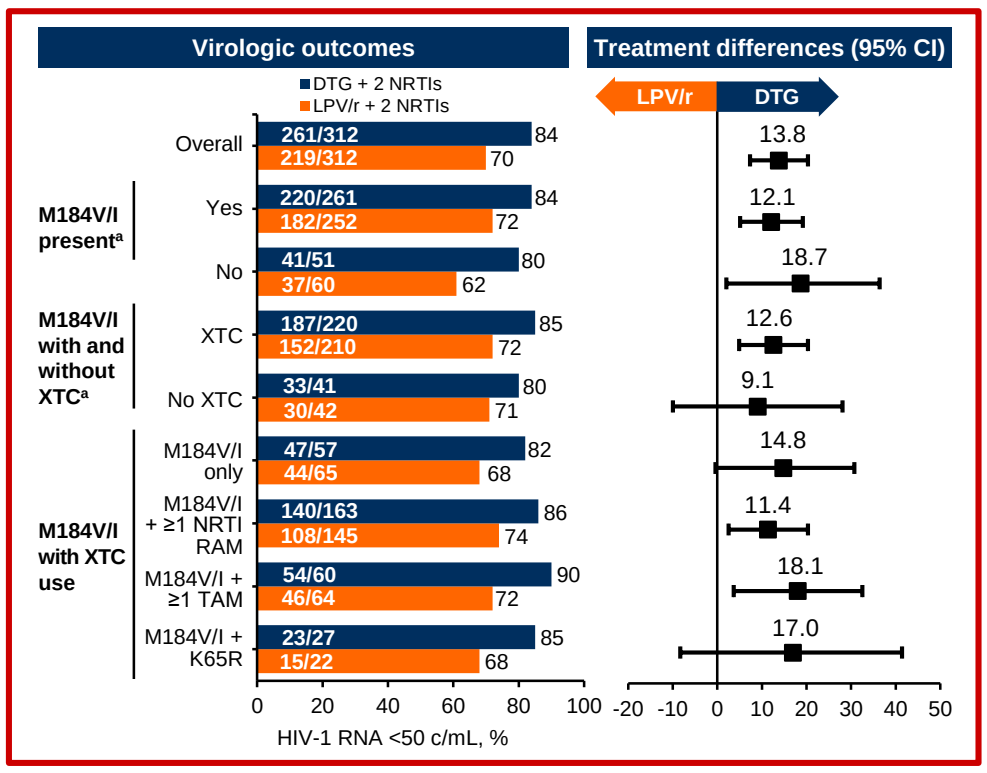
### Demographics and Baseline Characteristics

- In 624 participants, baseline characteristics were well balanced between the DTG + 2 NRTI (n=312) and LPV/r + 2 NRTI (n=312) treatment groups
  - Mean age (range) was 37.5 (19-64) vs 38.7 (18-72) years, mean HIV-1 RNA was 4.2 log c/mL for both, and mean duration of first antiretroviral (ARV) regimen was 37 vs 35 months, respectively[1]
- NRTI background regimen included 3TC or FTC in 86% and 87% of participants in the DTG and LPV/r groups, respectively
- At baseline, M184V/I was present in 84% of the DTG group and 81% of the LPV/r group[1]
  - 3TC or FTC was used in 71% (220/312) and 67% (210/312) of these participants in the DTG and LPV/r groups, respectively

### Snapshot Outcomes and Analysis at Week 48

- Overall, 84% (261/312) of participants on DTG vs 70% (219/312) on LPV/r achieved HIV-1 RNA <50 c/mL at Week 48 (adjusted difference 13.8%; 95% confidence interval [CI]: 7.3-20.3; *P*<0.001 for superiority)
- Response rates were consistently higher for the DTG arm regardless of the presence of M184V/I and use or not of 3TC or FTC (Figure 1)

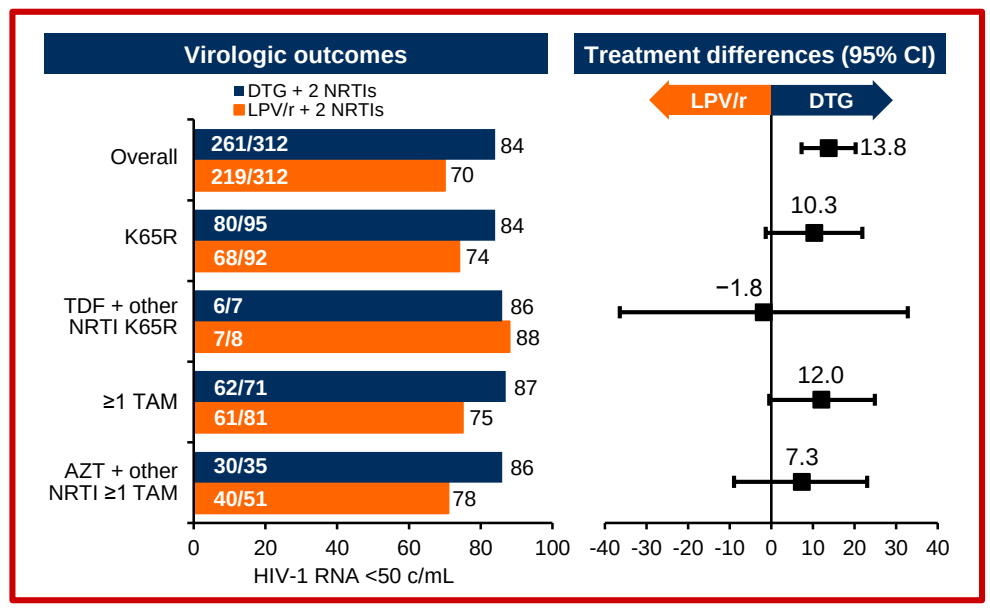
**Figure 1. Response Rates by Presence of M184V/I at Baseline With or Without Additional NRTI Mutations at Week 48: ITT-E Analysis.**




ITT-E, intention-to-treat–exposed; RAM, resistance-associated mutation; TAM, thymidine analogue mutation; XTC, 3TC or FTC. [a]M184V/I alone or plus additional NRTI mutations.

- Virologic nonresponse was observed in 10% and 22% of participants in the DTG and LPV/r arm, respectively, and 9% and 19% in the subset of participants with M184V/I and either 3TC or FTC use, respectively
- High responses were also observed in the DTG arm, when zidovudine or tenofovir disoproxil fumarate were included in the baseline regimen in the presence of thymidine analogue mutations or K65R, respectively; however, participant numbers in these subgroups were small (Figure 2)

**Figure 2. Snapshot Outcomes by Key Baseline Subgroups at Week 48: ITT-E by TDF Use With K65R and AZT Use With TAMs.**




ITT-E, intention-to-treat–exposed; TAM, thymidine analogue mutation.

### Confirmed Virologic Withdrawals Through Week 48

- Among the 11 (4%) confirmed virologic withdrawals (CVWs) in the DTG group, 5/11 (45%) had M184V/I at baseline with use of 3TC or FTC[1]
- Among the 30 (10%) CVWs in the LPV/r group, 15/30 (50%) had M184V/I at baseline with use of 3TC or FTC[1]
- Emergent resistance mutations were observed in 2 participants in the DTG group and 3 in the LPV/r group (Table)[1]

**Table. Resistance Mutations in Participants with CVW[1]**

| Group | HIV subtype | CVW visit | NRTI use | BL VL | CVW VL | BL NRTI RAM | Emergent RAMs |
|---|---|---|---|---|---|---|---|
| DTG | B | Wk 36 | FTC + TDF | 461,801 | 2464 | K219K/E, M184V | INSTI: G118R NRTI: D67N |
| | C | Wk 48 | 3TC + AZT | 1,248,517 | 454 | K70E, M184V | INSTI: H51H/Y, G118R, E138E/K, R263R/K |
| LPV/r | A | Wk 24 | 3TC + TDF | 583,004 | 452 | None | NRTI: K70K/R, M184V |
| | F/B | Wk 24 | AZT + 3TC | 12,231 | 835 | K219K/E, K65R, K70K/E, M184V | NRTI: K219K/Q |
| | C | Wk 48 | AZT + 3TC | 20,356 | 3141 | A62A/V, D67D/N, K65K/R, K70K/E/Q, M184W | NRTI: K70K/Q/R, K219K/E |

BL, baseline; RAM, resistance-associated mutation.

## Conclusions

- Week 48 results demonstrated superior efficacy (adjusted treatment difference, 13.8%; 95% CI, 7.3-20.3; *P*<0.001) of DTG + 2 NRTIs vs LPV/r + 2 NRTIs
- Response rates were high in participants receiving DTG + 2 NRTIs regardless of pre-existing resistance to one of the NRTIs in the background regimen, including when 3TC or FTC was used in the presence of M184V/I
- Rates of virologic failure were lower in the DTG arm regardless of baseline NRTI resistance patterns and second-line background NRTI use
- WHO interim guidelines with updated recommendations for first- and second-line ARV therapy now include DTG + 2 NRTIs as a recommended second-line treatment option for patients failing an NNRTI or protease inhibitor first-line ARV regimen[2]

**Acknowledgments:** This study was funded by ViiV Healthcare. We thank everyone who has contributed to the DAWNING study, including study participants and their families, clinical investigators and their site team members, and the ViiV Healthcare and GlaxoSmithKline study teams. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare. These data have been previously presented in full at the Conference on Retrovirus and Opportunistic Infections; March 4-7, 2019; Seattle, WA. Abstract 144.

**References: 1.** Aboud M et al. *Lancet Infect Dis.* 2019;19:253-264. **2.** World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1. Accessed March 13, 2019.