# Durable Suppression and Low Rate of Virologic Failure 3 Years After Switch to DTG + RPV 2-Drug Regimen: SWORD-1 and -2 Studies

P060

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## Introduction

- As individuals with HIV live longer, reducing exposure to antiretroviral therapy (ART) is a potential strategy to limit ART-related comorbidity[1]
- Because of its potency, safety, and resistance barrier, DTG has been shown to be an effective core agent for 2-drug regimens (2DRs)[2]
  - The virologic efficacy and safety profiles of RPV make it an ideal NRTI-sparing 2DR partner[3]
- SWORD-1 and SWORD-2 demonstrated efficacy of DTG + RPV, which was non-inferior (−8% margin) to continuing current 3DR at Week 48[4]
- We present pooled data from SWORD-1 and SWORD-2 for treatment with DTG + RPV through Week 148. Data for CAR treatment have been presented elsewhere[4]

## Methods

### Study Design

- SWORD-1 and SWORD-2 are identically designed, multicenter, open-label, parallel-group, non-inferiority, phase III studies; participants with baseline HIV-1 RNA <50 c/mL taking INSTI, NNRTI, or PI + 2 NRTIs were randomized 1:1 to switch to DTG + RPV or to continue CAR; those who continued CAR and were suppressed switched to DTG + RPV at Week 52 (a full description of the methods has been previously reported)[4]
  - Participants can complete the study at any point after the Week 148 visit

### Study Populations

- Participants randomized to DTG + RPV on Day 1 who received at least 1 dose of DTG + RPV (Early-Switch group)
- Participants randomized to continue CAR on Day 1, completed the Early-Switch phase at Week 52, and received at least 1 dose of DTG + RPV upon switching at Week 52 (Late-Switch group)

## Results

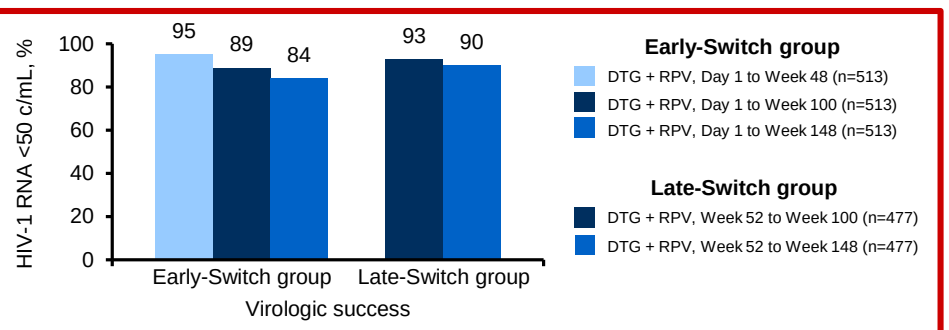
### Study Disposition

- Overall, 990 participants received DTG + RPV treatment (Early-Switch group, n=513; Late-Switch group, n=477)

### Virologic Efficacy

- Through 148 weeks of treatment, DTG + RPV continued to be efficacious in the Early-Switch group (Figure 1)
  - Virologic efficacy in the Late-Switch group at Week 148 was similar to that in the Early-Switch group at Week 100[5]

**Figure 1. HIV-1 RNA <50 c/mL (FDA Snapshot) at Weeks 48, 100, and 148**




| n (%) | Early-Switch group: DTG + RPV Week 48 (n=513) | Early-Switch group: DTG + RPV Week 100 (n=513) | Early-Switch group: DTG + RPV Week 148 (n=513) | Late-Switch group: DTG + RPV Week 100 (n=477) | Late-Switch group: DTG + RPV Week 148 (n=477) |
|---|---|---|---|---|---|
| **Virologic success** | 486 (95) | 456 (89) | 432 (84) | 445 (93) | 428 (90) |
| **Virologic non-response** | 3 (<1) | 13 (3) | 14 (3) | 8 (2) | 11 (2) |
| Data in window, not <50 c/mL | 0 | 5 (<1) | 1 (<1) | 3 (<1) | 4 (<1) |
| Discontinued for lack of efficacy | 2 (<1) | 7 (1) | 12 (2) | 3 (<1) | 4 (<1) |
| Discontinued while not <50 c/mL | 1 (<1) | 1 (<1) | 1 (<1) | 0 | 0 |
| Change in ART | 0 | 0 | 0 | 2 (<1) | 3 (<1) |
| **No virologic data** | 24 (5) | 44 (9) | 67 (13) | 24 (5) | 38 (8) |
| Discontinued because of AE or death | 17 (3) | 27 (5) | 40 (8) | 11 (2) | 17 (4) |
| Discontinued for other reasons | 7 (1) | 17 (3) | 25 (5) | 10 (2) | 19 (4) |
| Missing data during window but on study | 0 | 0 | 2 (<1) | 3 (<1) | 2 (<1) |

- Through Week 148, there was a low number of confirmed virologic withdrawals (CVWs) across study populations who received DTG + RPV (1%; 11/990)
  - 3 of these CVWs (<1%) occurred between the Week 100 analysis and Week 148 (Table 1)
- CVWs with resistance-associated mutations (RAMS) were low across both groups and were detected in 6 (0.6%) participants
  - RAMs were not detected at baseline in 4 of these participants; in 2 participants, GenoSure testing was not available at baseline
  - No participants had INSTI RAMs at CVW time point; 1 participant with only polymorphic INSTI V151V/I (no impact on DTG susceptibility) had INSTI RAM mixtures N155N/H and G163G/R at baseline

### Safety and Tolerability

- Low rates of grade 2 to 4 drug-related AEs and serious AEs were reported (Table 2)
  - The majority of AEs were grade 1 or 2
- There were 4 drug-related SAEs; all started before Week 48

**Table 1. Confirmed Virologic Withdrawals From Week 100 to Week 148 in Participants Exposed to DTG + RPV**

| Week of failure | Previous regimen | Viral loads, copies/mL[b] | Resistance mutations[a]: Baseline (GenoSure[c]) NNRTI | Baseline (GenoSure[c]) INSTI | Confirmed virologic withdrawal NNRTI | Confirmed virologic withdrawal INSTI | Fold change: DTG | Fold change: RPV |
|---|---|---|---|---|---|---|---|---|
| W112 | RAL/TDF/FTC | 118; 230; 324 | None | E157Q, G193E, T97T/A | M230M/L | E157Q, G193E | 1.47 | 2 |
| W112 | DRV, RTV, TDF/FTC | 148; 307; 219 | ND[d] | | ND[d] | | ND[d] | |
| W136[e] | EFV/TDF/FTC | 4294; 7247; 40,020; 3378 | NR[f] | | E138A, L100L/I | NR[f] | — | 4.14 |

ND, not determined; NR, not reported. [a]Shading represents participants with NNRTI RAMs. [b]Underlined value denotes viral load when participant met virologic withdrawal. [c]HIV-1 baseline resistance testing was performed on integrated HIV-1 proviral DNA using GenoSure Archive® assay (Monogram Biosciences, South San Francisco, CA). On-study resistance testing used standard plasma-based genotypic and phenotypic resistance testing. [d]Sample not sent for resistance testing because of low viral load that was below the assay cutoff. [e]Participant in the Late-Switch group. [f]Sample failed testing.

**Table 2. Adverse Events at Weeks 48, 100, and 148**

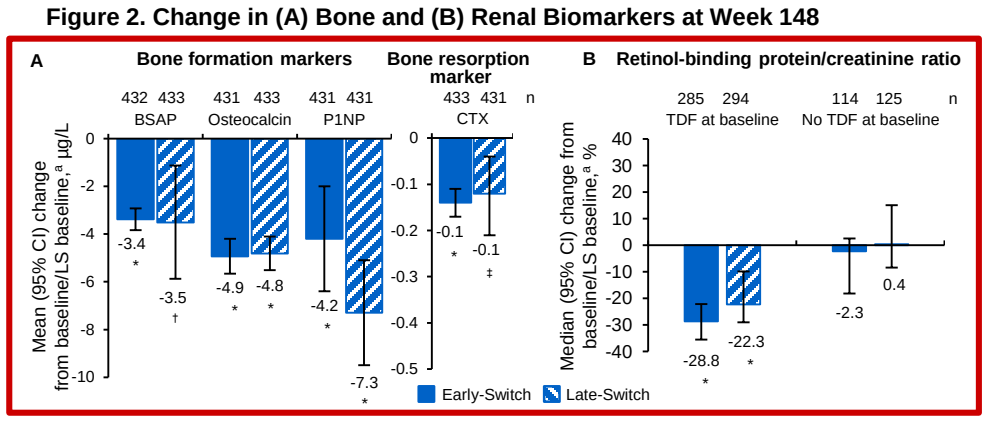
| n (%) | Early-Switch group: DTG + RPV Week 48 (n=513) | Early-Switch group: DTG + RPV Week 100[a] (n=513) | Early-Switch group: DTG + RPV Week 148 (n=513) | Late-Switch group: DTG + RPV Week 100[a] (n=477) | Late-Switch group: DTG + RPV Week 148 (n=477) |
|---|---|---|---|---|---|
| Any AE | 395 (77) | 453 (88) | 472 (92) | 386 (81) | 419 (88) |
| Any AE occurring in ≥10% of participants in any group | | | | | |
| Nasopharyngitis[b] | 49 (10) | 8 (2) | 100 (19) | 8 (2) | 76 (16) |
| Headache | 41 (8) | 59 (12) | 65 (13) | 29 (6) | 37 (8) |
| Upper respiratory tract infection[b] | 24 (5) | 51 (10) | 63 (12) | 35 (7) | 47 (10) |
| Diarrhea | 32 (6) | 46 (9) | 52 (10) | 21 (4) | 29 (6) |
| Viral upper respiratory tract infection[b] | 1 (<1) | 77 (15) | 6 (1) | 49 (10) | 10 (2) |
| Drug-related grade 2-4 AEs | 29 (6) | 29 (6) | 31 (6) | 13 (3) | 16 (3) |
| Serious AEs | 27 (5) | 58 (11) | 71 (14) | 30 (6) | 43 (9) |
| Fatal AEs | 1 (<1) | 1 (<1) | 3 (<1) | 0 | 0 |
| AEs leading to discontinuation[c] | 17 (3) | 34 (7) | 42 (8) | 15 (3) | 19 (4) |
| Psychiatric disorders[d] | 7 (1) | 12 (2) | 15 (3) | 5 (1) | 7 (1) |

[a]Data up to Week 100 database cutoff date are included. [b]Preferred term coding based on MedDRA version 19.1 for Week 48 analysis, 20.1 for Week 100 analysis, and 21.0 for Week 148 analysis; the terms "cold" and "common cold" underwent a change in dictionary coding between Week 48 (from nasopharyngitis) to Week 100 (viral upper respiratory tract infection) to Week 148 (nasopharyngitis). [c]Includes all AEs, regardless of relationship to study drug; a participant may have had >1 AE that led to discontinuation. [d]Grouped term includes multiple AEs.

### Change From Baseline/Late-Switch Baseline in Biomarkers at Week 148

- Decreases in all measured bone turnover biomarkers for both Early-Switch and Late-Switch groups and in retinol-binding protein/creatinine ratio in participants with prior TDF exposure were observed (Figure 2)

**Figure 2. Change in (A) Bone and (B) Renal Biomarkers at Week 148**




BSAP, bone-specific alkaline phosphatase; CTX, type I collagen C-telopeptide; LS, Late-Switch; P1NP, procollagen 1 N-terminal propeptide. [a]Last pre-switch data (usually Week 48) used for LS baseline. *$P$<0.001 vs baseline/LS baseline. †$P$=0.004 vs baseline/LS baseline. ‡$P$=0.008 vs baseline/LS baseline.

- No change was observed in eGFR by cystatin C irrespective of pre-switch TDF exposure for both Early-Switch and Late-Switch groups at Week 148 (median change in both groups, 0.00 mL/min/1.73 $m^2$)
- Minimal changes in median total cholesterol:HDL cholesterol ratio, HDL cholesterol, LDL cholesterol, and triglycerides occurred from baseline/Late-Switch baseline to Week 148

## Conclusions

- Switching participants from 3DR to the 2DR DTG + RPV was associated with maintenance of viral suppression, low frequency of CVWs, few observations of NNRTI RAMs, and no INSTI RAMs over treatment for 3 years in the Early-Switch group and over 2 years in the Late-Switch group
- After 148 weeks, DTG + RPV showed a good safety profile with few serious AEs and grade 3 or 4 AEs. Biomarker data indicate reduced bone turnover after the switch to DTG + RPV, with significant improvements in renal tubular function for those patients switching from a TDF-containing regimen
- DTG + RPV has demonstrated durable efficacy, is well tolerated, and offers an HIV treatment option with less cumulative ART exposure in select virologically suppressed patients

**Acknowledgments:** This study was funded by ViiV Healthcare. We thank everyone who has contributed to the success of these studies, including all study participants and their families; the SWORD-1 and SWORD-2 clinical investigators and their staff; and the ViiV Healthcare, GSK, and Janssen 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. Data included in this poster have been previously presented in full at the 25th Annual Conference of the British HIV Association; April 2-5, 2019; Bournemouth, UK; Poster P008.

**References: 1.** Raffi et al. *HIV Med.* 2016;17(suppl 5):3-16. **2.** Cahn et al. *Lancet.* 2019;393:143-155. **3.** Cohen et al. *J Acquir Immune Defic Syndr.* 2012;60:33-42. **4.** Llibre et al. *Lancet.* 2018;391:839-849. **5.** Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Poster THPEB047.

**HIV & Hepatitis in the Americas Congress; April 4-6, 2019; Bogotá, Colombia**