

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

P008

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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 comorbidity¹
- 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 partner³
- SWORD-1 and SWORD-2 demonstrated efficacy of DTG + RPV, which was non-inferior (-8% margin) to continuing current 3DR at Week 48⁴
- 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 elsewhere⁴

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

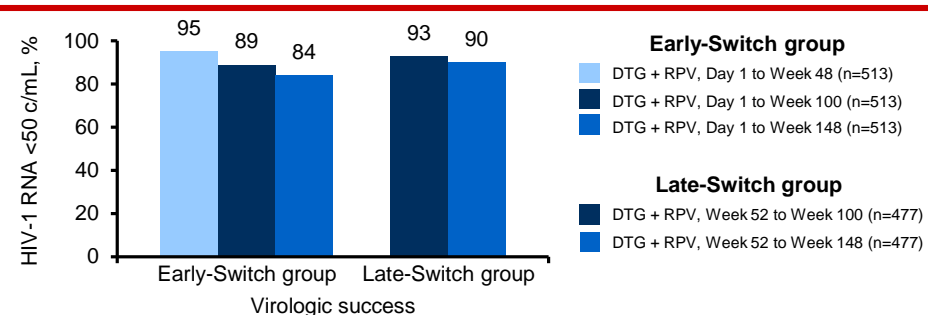
Study Disposition

- 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 100⁵

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



n (%)	Early-Switch group			Late-Switch group	
	DTG + RPV Week 48	DTG + RPV Week 100	DTG + RPV Week 148	DTG + RPV Week 100	DTG + RPV Week 148
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				Fold change	
			Baseline (GenoSure ^c)		Confirmed virologic withdrawal		DTG	RPV
			NNRTI	INSTI	NNRTI	INSTI		
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. ^aShading represents participants with NNRTI RAMs. ^bUnderlined value denotes viral load when participant met virologic withdrawal. ^cHIV-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. ^dSample not sent for resistance testing because of low viral load that was below the assay cutoff. ^eParticipant in the Late-Switch group. ^fSample failed testing.

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

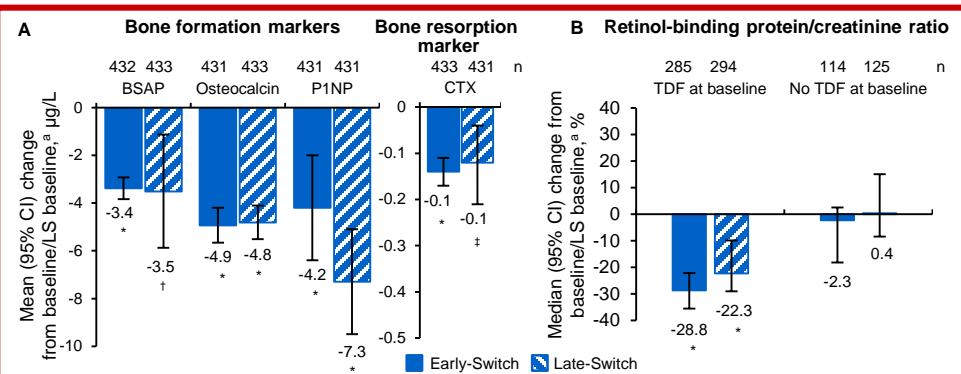
n (%)	Early-Switch group			Late-Switch group	
	DTG + RPV Week 48 (n=513)	DTG + RPV Week 100 ^a (n=513)	DTG + RPV Week 148 (n=513)	DTG + RPV Week 100 ^a (n=477)	DTG + RPV Week 148 (n=477)
Any AE	395 (77)	453 (88)	472 (92)	386 (81)	419 (88)
Any AE occurring in ≥10% of participants in any group					
Nasopharyngitis ^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)

^aData up to Week 100 database cutoff date are included. ^bPreferred 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). ^cIncludes all AEs, regardless of relationship to study drug; a participant may have had >1 AE that led to discontinuation. ^dGrouped 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. ^aLast 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 m²)
- 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

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