Durable Suppression 2 Years After Switch to Dolutegravir + Rilpivirine 2-Drug Regimen: SWORD-1 and SWORD-2 Studies

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Australasian HIV&AIDS Conference; September 24-26, 2018; Sydney, Australia

Disclosures of Interest

- M Aboud, L Kahl, E Blair, M Underwood, B Wynne, M Gartland, and K Smith are employees of ViiV Healthcare and own stock in GlaxoSmithKline
- C Orkin reports grants from ViiV Healthcare during the conduct of the study and grants, personal fees, nonfinancial support and other from Gilead, Janssen, AbbVie, BMS, ViiV Healthcare, and MSD outside the submitted work
- D Podzamczer has received research grants and/or honoraria for advisories and/or conferences from ViiV Healthcare, Gilead, Janssen, and Merck outside the submitted work
- J Bogner reports personal fees from ViiV Healthcare, Gilead, Merck Sharp & Dohme, Janssen, and Hexal outside the submitted work
- D Baker reports grants from ViiV Healthcare during the conduct of the study and reports grants, personal fees, and nonfinancial support from ViiV Healthcare and Gilead and personal fees from MSD outside the submitted work
- M-A Khuong-Josses and D Parks have nothing to disclose
- K Angelis is an employee and shareholder of GlaxoSmithKline
- K Vandermeulen is an employee and shareholder of Janssen Pharmaceutica NV

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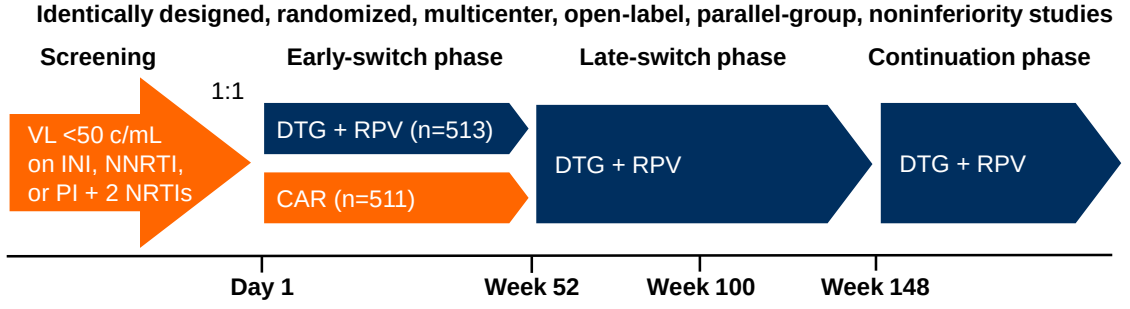
Introduction

- The requirement for lifelong ART for HIV infection has highlighted a need to limit ART-related cormorbidity[1]
- The potency, safety, and resistance barrier of dolutegravir (DTG) make it an ideal core agent for 2-drug regimens
- The SWORD-1 and SWORD-2 studies evaluated whether a 2-drug regimen of DTG + rilpivirine (RPV) once daily was as effective as a 3- or 4-drug regimen for the maintenance of virologic suppression[2]
  - 48-week data showed that switching to DTG + RPV demonstrated high efficacy and was noninferior to the continuation of a 3- or 4-drug regimen in virologically suppressed HIV-1–infected adults
- We present the combined analysis of SWORD-1 and SWORD-2 at Week 100, which includes data from participants who switched at Week 52

1. Raffi et al. *HIV Med.* 2016;17(suppl 5):3-16. **2.** Llibre et al. *Lancet*. 2018;391:839-849.

SWORD-1 and SWORD-2 Phase III Study Design

- SWORD-1 and SWORD-2 were identically designed, randomized, multicenter, open-label, parallel-group, noninferiority phase III studies
  - A full description of the study design, including eligibility criteria and endpoints, has been previously reported



Llibre et al. *Lancet*. 2018;391:839-849.

Study Populations and Study Disposition

- Early-switch group: Participants randomized to DTG + RPV on Day 1 who received at least 1 dose of DTG + RPV
- Late-switch group: Participants randomized to continue their current antiretroviral regimen (CAR) on Day 1, completed early-switch phase at Week 52, and received at least 1 dose of DTG + RPV upon switching at Week 52
- Of 1024 participants randomized and treated with DTG + RPV or CAR, 892 (87%) completed the Week 100 study visit
  - Demographics and baseline characteristics have been previously reported

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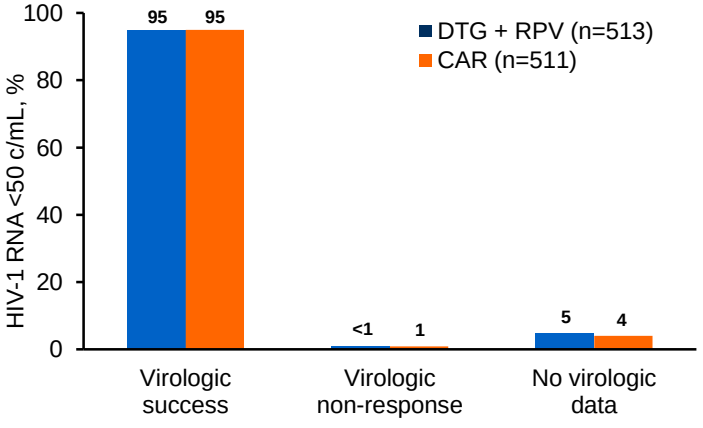
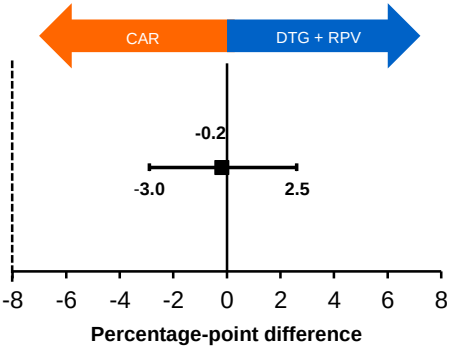
Snapshot Outcomes at Week 48 (Pooled)

Virologic outcomes



Adjusted treatment difference (95% CI)[a]



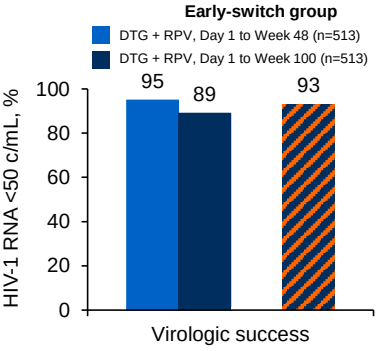
DTG + RPV is **non-inferior** to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48

[a]Adjusted for age and baseline 3rd agent.

Llibre et al. Lancet. 2018;391:839-849

Virologic Efficacy

- Through 100 weeks of treatment, DTG + RPV continued to be efficacious in the early-switch group
  - Virologic efficacy in the late-switch group at Week 100 was similar to that of the early-switch group at Week 48



n, %	Early-switch group: DTG + RPV Week 48	Early-switch group: DTG + RPV Week 100	Late-switch group: DTG + RPV Week 100
Virologic success	486 (95)	456 (89)	444 (93)
Virologic nonresponse	3 (<1)	13 (3)	10 (2)
Data in window, not <50 c/mL	0	5 (<1)	3 (<1)
Discontinued for lack of efficacy	2 (<1)	7 (1)	3 (<1)
Discontinued while not <50 c/mL	1 (<1)	1 (<1)	0
Change in ART	0	0	4 (<1)
No virologic data	24 (5)	44 (9)	23 (5)
Discontinued because of AE or death	17 (3)	27 (5)	11 (2)
Discontinued for other reasons[a]	7 (1)	17 (3)	9 (2)
Missing data during window but on study	0	0	3 (<1)

[a]Other reasons for discontinuation while treated with DTG + RPV were lost to follow-up, n=3; protocol deviation, n=5 (prohibited medication use, n=3; pregnancy, n=2); withdrawal of consent, n=18 (participant relocated, n=5; travel burden, n=2; other, n=9); and investigator discretion, n=2.

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NNRTI Resistance-Associated Mutations

- Through Week 100, there was a low number of confirmed virologic withdrawals across study populations (1%; 10/990) - HIV RNA ≥ 50 c/mL, retest ≥ 200 c/mL
  - 2 occurred in the CAR arm (to week 52)
  - 6 occurred in the Early Switch group DTG+RPV (week 1-100)
  - 2 occurred in the Late Switch group DTG+RPV (week 52 – 100)
- CVWs with resistance-associated treatment-emergent mutations were low across both groups and detected in 3 participants, all receiving DTG + RPV (0.3%; 3/990)
  - In all 3 participants, at least 1 NNRTI resistance–associated mutation was detected

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DTG + RPV: Low Rates of Confirmed Virologic Withdrawal Through Week 100

Week of failure	Previous regimen	Viral loads, copies/mL[b]	Resistance mutations[a]		Fold change
			Baseline (GenoSure[c])	Confirmed virologic withdrawal	
Week 24	EFV/TDF/FTC	88; 466	NNRTI: none INSTI: G193E	NNRTI: none INSTI: G193E	DTG, 1.02
Week 36	EFV/TDF/FTC	1,059,771; 1018; <50	NNRTI: none INSTI: none	NNRTI: K101K/E INSTI: none	RPV, 1.21
Week 64[d]	DTG/ABC/3TC	833; 1174; <50	NNRTI: none INSTI: N155N/H, G163G/R	INSTI resistance test failed	————
Week 76[d]	ATV, ABC/3TC	79; 162; 217	————	Test not performed[e]	————
Week 88	DTG/ABC/3TC	278; 2571; 55	NNRTI: none INSTI: none	NNRTI: E138E/A INSTI: none	RPV, 1.61 DTG, 0.72
Week 88	RPV/TDF/FTC	147; 289	————	Test not performed[e]	————
Week 100	EFV/TDF/FTC	651; 1105; 300	NNRTI: K101E, E138A INSTI: G193E	NNRTI: K101E, E138A, M230M/L INSTI resistance test failed	RPV, 31
Week 100	ATV, RTV, TDF/FTC	280; 225; 154	NNRTI: none INSTI: none	NNRTI: none INSTI: none	————

[a]Shading represents participants with treatment-emergent NNRTI resistance–associated mutations. [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]Participants in the late-switch group. [e]Resistance testing not performed because of low viral load.

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Safety and Tolerability

- Cumulative AEs reported in the early-switch group were consistent with the respective ARV drugs

Adverse Events at Week 48 and Week 100

n (%)	Early-switch group: DTG + RPV Week 48 (n=513)	Early-switch group: DTG + RPV Week 100 (n=513)	Late-switch group: DTG + RPV Week 100 (n=477)
Any AE	395 (77)	453 (88)	386 (81)
Any AE occurring in ≥10% of participants in any group			
Viral upper respiratory tract infection[a]	—	77 (15)	49 (10)
Headache	41 (8)	59 (12)	29 (6)
Upper respiratory tract infection[a]	24 (5)	51 (10)	35 (7)
Nasopharyngitis[a]	49 (10)	8 (2)	8 (2)
Drug-related AEs	97 (19)	103 (20)	56 (12)
Drug-related AEs occurring in ≥2% of participants in any group[b]			
Headache	11 (2)	11 (2)	8 (2)
Nausea	7 (1)	8 (2)	5 (1)
Serious AEs	27 (5)	58 (11)	30 (6)
Fatal AEs	1 (<1)	1 (<1)	0
AEs leading to discontinuation[c]	17 (3)	34 (7)	15 (3)
Psychiatric disorders[d]	7 (1)	12 (2)	5 (1)

[a]Preferred term coding based on MedDRA version 20.1 rather than 19.1 used in the Week 48 analysis, wherein "cold" and "common cold" changed in preferred term from "nasopharyngitis" to "viral upper respiratory tract infection." [b]There were no grade 2-4 drug-related AEs of ≥2% frequency in any group. [c]A participant might have had >1 AE that led to discontinuation. [d]Grouped term includes multiple adverse events. Psychiatric AEs that led to discontinuation in the early-switch group were anxiety (n=4), suicidal ideation (n=4), insomnia (n=2), depression (n=2), affective disorder, depressed mood, nightmare, and completed suicide (n=1 each); those in the late-switch group were insomnia (n=3), depression (n=2), abulia, confusional state, loss of libido, major depression, and suicidal ideation (n=1 each).

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Biomarker Analyses

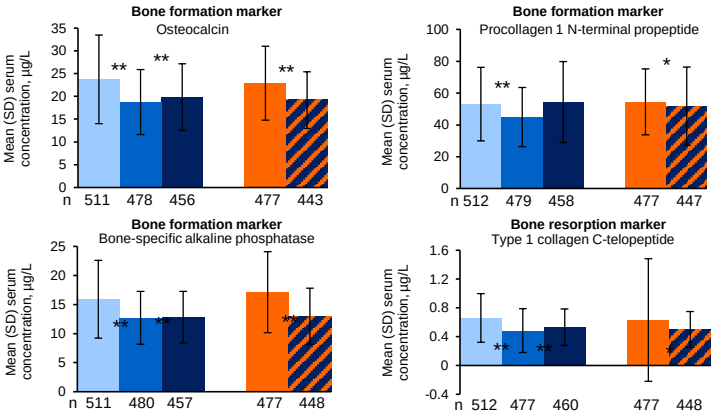
- All bone turnover biomarkers were decreased from baseline at Week 100 except procollagen 1 N-terminal propeptide in the early-switch group
- DTG + RPV was associated with a neutral effect on atherogenesis and inflammation biomarkers with no pattern of change noted at Week 100
  - No further changes at Week 100 compared with Week 48, as previously presented

Early-switch group

- DTG + RPV, Baseline
- DTG + RPV, Week 48
- DTG + RPV, Week 100

Late-switch group

- DTG + RPV, Baseline[a]
- DTG + RPV, Week 100



[a]Last pre-switch data (usually Week 48) used for late-switch baseline. *P<0.05 vs baseline. **P<0.001 vs baseline.

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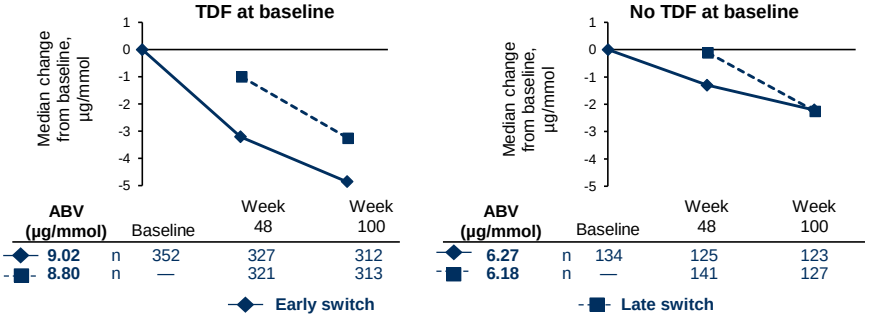
Biomarker Analyses (cont)

- Improvements in renal tubular function, as measured by changes from baseline in urine retinol-binding protein/creatinine ratio and urine beta-2 microglobulin/ creatinine ratio (not shown), were maintained at Week 100 in the early-switch group

Change From Baseline in Retinol-Binding Protein/Creatinine Ratios at Week 48 and Week 100



ABV, absolute baseline value (collected at baseline in the SWORD studies, before any treatment switch).

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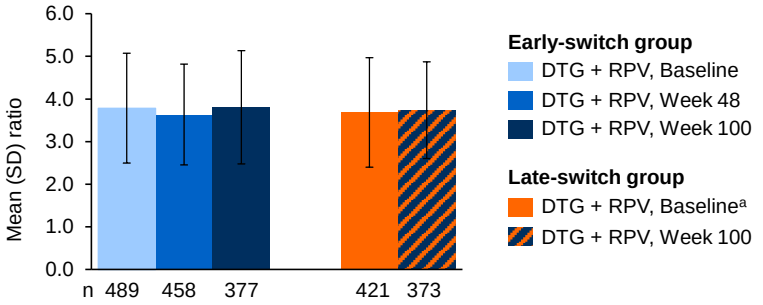
Biomarker Analyses (cont)

- No discernable pattern of changes from baseline in mean serum concentration of lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides) was noted in the early- or late-switch groups

Total Cholesterol/HDL Cholesterol Ratio at Week 48 and Week 100



[a]Last pre-switch data (usually Week 48) used for late-switch baseline.

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Conclusions

- Durable efficacy: high level of virologic suppression maintained through 100 weeks in the early-switch group
- Reproducible outcomes: 93% efficacy in the late-switch group (48 weeks after switching to DTG + RPV), consistent with 95% efficacy in the early-switch group at Week 48
- No CVWs with INSTI mutations; CVWs with NNRTI mutations rare (0.3%; 3/990 through Week 100), with minimal impact on future treatment options
- The combination of once-daily DTG + RPV was generally well tolerated
- DTG + RPV is associated with a favourable effect on renal tubular function, a neutral effect on surrogate biomarkers of atherogenesis and inflammation, and a significant improvement in biomarkers of bone health
- Data through Week 100 support efficacy and safety of switching to once-daily DTG + RPV for patients with HIV-1 on stable, suppressive 3- or 4-drug ART

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Acknowledgments

- 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

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Johnson
Orkin
Ustianowski

  - The ViiV Healthcare, GSK, and Janssen study teams

This study was funded by ViiV Healthcare.