Renal, Inflammatory and Bone Biomarkers Following Switch to the DTG + RPV 2-Drug Regimen: The SWORD-1 & SWORD-2 Studies

BPD2/10

C Orkin,[1] JM Llibre,[2] L Kahl,[3] E Blair,[4] B Wynne,[5] L Curtis,[6] K Angelis,[6] M Aboud,[3] M Gartland[4]

[1]Barts Health NHS Trust, London, UK; [2]Hospital Germans Trias i Pujol, Badalona, Spain; [3]ViiV Healthcare, Brentford, UK; [4]ViiV Healthcare, Research Triangle Park, NC, USA; [5]ViiV Healthcare, Collegeville, PA, USA; [6]GlaxoSmithKline, London, UK

Introduction

- 2-drug regimens (2DRs) are being evaluated for their ability to minimize cumulative drug exposure. Dolutegravir's (DTG's) potency, pharmacokinetics, safety, and resistance barrier make it an ideal core agent to partner with the pharmacokinetic properties of rilpivirine (RPV)
- We evaluated the effect of switching from 3- or 4-drug current antiretroviral therapy (CAR) to the nucleoside reverse transcriptase inhibitor–sparing 2DR DTG + RPV in 2 randomised phase III studies (SWORD-1 and SWORD-2) on renal function, atherogenesis, inflammation, and biomarkers of bone turnover

Methods

- SWORD-1 and SWORD-2 are identically designed, randomized, multicenter, open-label, phase III studies with demonstrated noninferior efficacy following switch of HIV-1-infected adults (<50 copies/mL for at least 6 months) from CAR to DTG + RPV once daily[1]
- Secondary study endpoints included change from Baseline to Week 48 for
  - Renal biomarkers: cystatin C, retinol binding protein, beta-2 microglobulin, and urine phosphate. CKD-EPI eGFR calculations (cystatin C) were also performed[2]
  - Mechanisms associated with atherogenesis and inflammation: C-reactive protein, D-dimer, fatty acid binding protein 2 (FABP2)
  - Biomarkers of bone resorption (type-1 collagen C-telopeptide) and bone formation (osteocalcin, procollagen 1-N-terminal propeptide, bone-specific alkaline phosphatase)
  - All biomarkers were quantitated on cryopreserved samples at the study central laboratory using standardized assays

Results

- 1024 participants across both studies were randomly assigned and exposed to DTG + RPV (n=513) or CAR (n=511)
- At Week 48, the percentage of participants who maintained viral load <50 copies/mL was 95% in both groups of the pooled SWORD-1 and SWORD-2 analysis (adjusted treatment difference, –0.2%; 95% CI, –3.0 to 2.5)
  - In addition, a subgroup analysis by baseline third-agent class showed consistent virologic efficacy results regardless of baseline third agent[3]
- Renal biomarkers: greater decreases were observed in the tubular biomarkers urine retinol binding protein, urine beta-2 macroglobulin, and urine phosphate in the 2DR vs CAR group (Table 1)
  - No change from Baseline was observed in the retinol binding protein/creatinine ratio or the beta-2 microglobulin/creatinine ratio in either group (irrespective of TDF at Baseline; Table 2)

Table 1. Renal Biomarkers: Change From Baseline to Week 48 (Pooled SWORD Data)

	DTG + RPV		CAR	
Renal biomarker	**n**	**Median (min, max)**	**n**	**Median (Min, Max)**
Cystatin C, mg/L				
Baseline	511	0.70 (0.3, 1.3)	505	0.70 (0.4, 1.3)
Week 48	483	0.00 (−0.4, 0.5)	482	0.00 (−0.4, 0.4)
Retinol binding protein (urine), nmol/L				
Baseline	487	5.61 (0.37, 190.50)	484	5.13 (0.37, 190.50)
Week 48	453	−1.87 (−189.98, 17.92)	455	−0.76 (−169.06, 186.72)
Beta-2 microglobulin (urine), nmol/L				
Baseline	319	14.41 (6.78, 11,271.22)	325	14.41 (6.78, 4830.52)
Week 48	161	−3.39 (−11,129.70, 125.42)	174	0.00 (−333.05, 3411.03)
Urine phosphate, mmol/L				
Baseline	486	19.70 (3.22, 81.40)	480	19.54 (3.22, 64.60)
Week 48	453	−0.65 (−66.86, 66.21)	453	−0.97 (−43.93, 59.76)

Table 2. Renal Biomarkers: Change From Baseline to Week 48 in Patients Receiving and Not Receiving TDF at Baseline (Pooled SWORD Data)

	DTG + RPV		CAR	
Renal biomarker	**n**	**Median (min, max)**	**n**	**Median (min, max)**
Retinol binding protein/creatinine ratio (urine), µg/mmol				
TDF at baseline				
Baseline	355	9.03 (1.8, 1320.8)	343	8.80 (1.6, 417.3)
Week 48	328	−3.21 (−1239.0, 14.9)	321	−1.00 (−224.7, 721.3)
No TDF at baseline				
Baseline	131	6.22 (1.4, 34.2)	141	6.18 (1.8, 303.4)
Week 48	123	−1.29 (−26.7, 13.0)	131	−0.12 (−250.1, 1067.7)
Beta-2 microglobulin/creatinine ratio (urine), mg/mmol				
TDF at baseline				
Baseline	225	0.017 (0.00, 14.32)	227	0.017 (0.00, 5.37)
Week 48	113	−0.004 (−14.16, 0.03)	124	0.002 (−0.32, 2.13)
No TDF at baseline				
Baseline	91	0.011 (0.00, 0.08)	96	0.011 (0.00, 1.76)
Week 48	47	0.001 (−0.02, 0.10)	50	−0.001 (−0.12, 2.07)

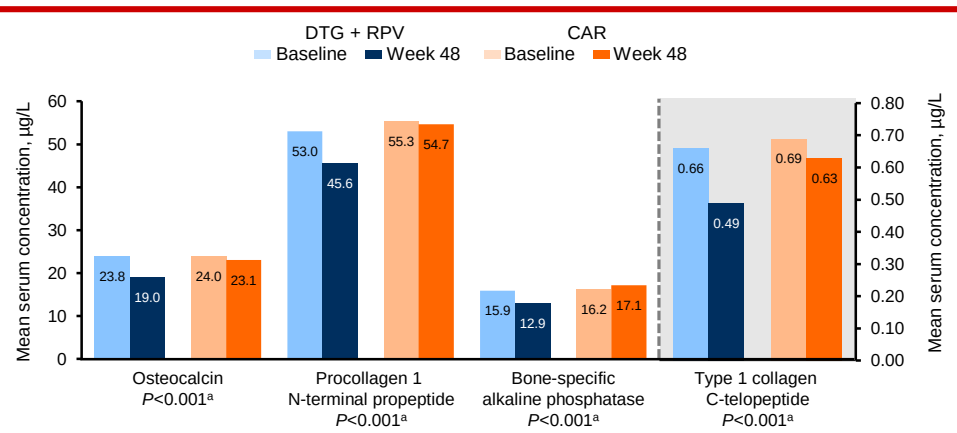
- There were no differences between groups or consistent pattern of change from Baseline to Week 48 in surrogate biomarkers for atherogenesis or inflammation (Table 3)
- The decrease in serum concentrations of bone turnover biomarkers, including bone-specific alkaline phosphatase, osteocalcin, procollagen type 1 N-propeptide, and type 1 collagen cross-linked C-telopeptide, from baseline to Week 48 in the DTG + RPV group differed significantly from the change observed from baseline to Week 48 in the CAR group (73% were switched from TDF to DTG + RPV at baseline) (*P*<0.001 for each biomarker; Figure 1)

Table 3. Atherogenesis and Inflammation Biomarkers: Change From Baseline to Week 48 (Pooled SWORD Data)

	DTG + RPV		CAR		Week 48 difference, DTG+RPV − CAR
Biomarker	**n**	**Mean (median [range])**	**n**	**Mean (median [range])**	**(95% CI)**
Inflammation					
C-RP, mg/L					
Baseline[a]	512	2.81 (1.3 [0.1, 34.4])	505	2.77 (1.3 [0.1, 33.8])	
Week 48	480	0.11 (0.0 [−32.7, 40.3])	482	0.47 (0.0 [−31.1, 96.0])	−0.36 (−1.2, 1.0)
IL-6, ng/L					
Baseline[a]	512	2.19 (1.6 [0.4, 15.1])	503	2.25 (1.57 [0.3, 34.5])	
Week 48	478	0.04 (−0.04 [−13.7, 25.8])	480	−0.12 (−0.05 [−32.8, 13.6])	0.16 (−0.2, 0.4)
Hypercoagulability					
D-dimer, nmol/L FEU					
Baseline[a]	504	1.87 (1.2 [1.0, 51.8])	496	1.80 (1.1 [1.0, 38.9])	
Week 48	463	−0.01 (0.0 [−19.9, 23.1])	466	−0.05 (0.0 [−37.8, 16.4])	0.04 (−0.28, 0.34)
Macrophage activation					
sCD163, µg/L					
Baseline[a]	509	590.48 (537.7 [176.0, 2036.9])	501	601.79 (555.4 [176.0, 1934.4])	
Week 48	477	57.99 (52.8 [−856.4, 1052.1])	477	54.10 (26.0 [−999.6, 1434.2])	3.89 (−22.4, 206.3)
Monocyte activation					
sCD14, ng/mL					
Baseline[a]	510	1703.31 (1677.5 [50.0, 3688.4])	502	1698.60 (1696.3 [50.0, 3381.8])	
Week 48	479	419.09 (363.7 [−1374.0, 3112.4])	479	778.15 (773.8 [−1571.3, 7569.2])	−359.06 (−451.7, 2325.5)
Endothelial dysfunction					
sVCAM-1, µg/L					
Baseline[a]	512	1933.50 (1894.6 [478.3, 4066.6])	503	1957.52 (1871.1 [776.1, 6106.9])	
Week 48	479	−2.43 (−21.5 [−3006.4, 9596.4])	480	63.57 (16.1 [−3983.1, 7594.6])	−66.00 (−190.8, 4180.9)
Fatty acid metabolism					
FABP2, ng/mL					
Baseline[a]	512	2.97 (2.3 [0.2, 23.7])	501	2.92 (2.37 [0.3, 19.3])	
Week 48	478	−2.13 (−1.5 [−22.1, 2.7])	478	−1.47 (−1.0 [−14.2, 4.7])	−0.66 (−0.9, 0.3)

CI, confidence interval; C-RP, C-reactive protein; FABP2, fatty acid binding protein-2; FEU, fibrinogen equivalent unit; sCD14, soluble cluster of differentiation 14; sCD163, soluble cluster of differentiation 163; SD, standard deviation; sVCAM-1, soluble vascular adhesion molecule 1. [a]Baseline values are actual values.

Figure 1. Bone Turnover Biomarkers: Change From Baseline to Week 48



[a]*P* values are from an ANCOVA model adjusting for original ART third-agent class, age, sex, body mass index category, smoking status, and baseline biomarker level.

Discussion

- Decreases in renal biomarkers (RBP and beta-2 microglobulin) indicate that this 2DR had a favorable effect on renal tubular function. Additionally, CKD-EPI eGFR (cystatin C) confirmed that switch to this 2DR had no effect on glomerular filtration rate
- The switch to the 2DR of DTG + RPV showed no statistically significant difference in surrogate biomarkers of atherogenesis and inflammation between baseline and Week 48 compared with the 3- or 4-drug antiretroviral therapies
- The greater reduction in bone turnover biomarkers observed in the DTG + RPV group suggests less bone remodeling (turnover) on this 2DR and is consistent with the improved bone mineral density reported for participants taking DTG + RPV in the dual-energy x-ray absorptiometry substudy of SWORD-1 and SWORD-2[4]

Conclusions

- DTG + RPV is associated with a favorable effect on renal tubular function, a neutral effect on surrogate biomarkers of atherogenesis and inflammation, and a significant improvement in biomarkers of bone health compared with a standard 3- or 4-drug regimen while preserving virologic suppression

Acknowledgments: This study was sponsored by ViiV Healthcare. Rilpivirine was supplied by Janssen Products, LP. The authors thank the study participants, their families and caregivers, and the study investigators for participation in the SWORD-1 and SWORD-2 studies. 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.

References: 1. Llibre et al. CROI 2017; Seattle, WA. Abstract 2421. **2.** Inker et al. *N Engl J Med.* 2012;367:20-29. **3.** Orkin et al. EACS 2017; Milan, Italy. Poster BPD1/5. **4.** McComsey et al. IAS 2017; Paris, France. Poster TUPDB0205LB.