

CADTH COMMON DRUG REVIEW

# Clinical Review Report

**DOLUTEGRAVIR / RILPIVIRINE (JULUCA)**

(ViiV Healthcare)

Indication: As a complete regimen to replace the current antiretroviral regimen for the treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA less than 50 copies per mL)

Service Line:	CADTH Common Drug Review
Version:	Final Clinical Review Report (With Redactions)
Publication Date:	June 2018
Report Length:	74 Pages

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**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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## Abbreviations

<b>3TC</b>	lamivudine
<b>AE</b>	adverse event
<b>ABC</b>	abacavir
<b>ARV</b>	antiretroviral
<b>BMD</b>	bone mineral density
<b>cAR</b>	current antiretroviral regimen
<b>CI</b>	confidence interval
<b>DHHS</b>	US Department of Health and Human Services
<b>DTG</b>	dolutegravir
<b>DXA</b>	dual-energy X-ray absorptiometry
<b>EFV</b>	efavirenz
<b>eGFR</b>	estimated glomerular filtration rate
<b>EQ-5D-5L</b>	EuroQol 5-Dimensions 5-Levels questionnaire
<b>FTC</b>	emtricitabine
<b>HCV</b>	hepatitis C virus
<b>INSTI</b>	Integrase strand transfer inhibitor
<b>ITT</b>	intention-to-treat
<b>ITT-E</b>	intention-to-treat exposed
<b>NI</b>	noninferiority
<b>NNRTI</b>	non-nucleoside reverse transcriptase inhibitor
<b>NRTI</b>	nucleoside reverse transcriptase inhibitor
<b>PI</b>	protease inhibitor
<b>PP</b>	per-protocol
<b>RNA</b>	ribonucleic acid
<b>RPV</b>	rilpivirine
<b>SAE</b>	serious adverse event
<b>SD</b>	standard deviation
<b>STR</b>	single-tablet regimen
<b>TAF</b>	tenofovir alafenamide
<b>TDF</b>	tenofovir disoproxil fumarate
<b>WDAE</b>	withdrawal due to adverse event

<b>Drug</b>	dolutegravir/rilpivirine (Juluca)
<b>Indication</b>	As a complete regimen to replace the current antiretroviral regimen for the treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA less than 50 copies per mL)
<b>Reimbursement Request</b>	As per indication
<b>Dosage Form(s)</b>	Dolutegravir 50 mg/ rilpivirine 25 mg fixed-dose combination
<b>NOC Date</b>	May 18, 2018
<b>Manufacturer</b>	ViiV Healthcare ULC

## Executive Summary

### Introduction

Triple antiretroviral (ARV) therapy, consisting of a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) anchored by a third drug from either the non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI) class, is the current standard of care for the initial treatment of HIV-1 infection.<sup>1</sup> The primary goal of ARV therapy is to suppress HIV-1 ribonucleic acid (RNA) below detectable limits (typically fewer than 50 copies/mL). Other goals of therapy follow from maximal viral load suppression and include restoration and improvement of immune function; enhanced quality and quantity of life-years; and reduced risks of HIV-related complications, virus transmission, and death.<sup>1</sup> ARV therapy is a lifelong commitment, requiring high levels of sustained treatment adherence. To simplify medication-taking and support long-term adherence, six single-tablet regimens (STRs) have been developed and marketed<sup>2,3</sup> alongside other non-STRs,<sup>1</sup> providing clinician and patient with an array of therapeutic options from which to choose. While there is no therapeutic need that is unmet by current ARV therapies according to the clinical expert consulted for this review, there has been some interest in simplifying or stepping down ARV regimens once maximal viral load suppression has been achieved.<sup>4,5</sup> Reasons for this include improving convenience (e.g., no requirement for co-administration with food, reduced pill burden), preventing drug–drug interactions, improving tolerability and minimizing exposure to treatment-related toxicity, and reducing treatment cost.<sup>1,5</sup> This has given rise to the step-down concept, in which a patient on a maximally effective, virologically suppressive, stable triple-ARV regimen is switched to a more simplified (e.g., dual) ARV regimen.<sup>5,6</sup> According to the *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living With HIV* issued by the US Department of Health and Human Services (DHHS),<sup>1</sup> maintaining virologic suppression without compromising future treatment options is of the utmost importance when considering a switch from a virologically suppressive ARV regimen to another, more simplified ARV regimen. For switching to a two-drug regimen, the DHHS guidelines include two regimen options that it considers to have good supporting evidence: 1) a boosted PI plus emtricitabine or lamivudine, or 2) dolutegravir plus rilpivirine.<sup>1</sup> Switching to a monotherapy regimen is not recommended due to a lack of efficacy and development of treatment resistance.<sup>1</sup>

## Indication under review

As a complete regimen to replace the current antiretroviral regimen for the treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA less than 50 copies per mL)<sup>7</sup>

## Reimbursement criteria requested by sponsor

As per indication

The objective of this systematic review was to evaluate the beneficial and harmful effects of Juluca, a fixed-dose combination of dolutegravir (an INSTI) plus rilpivirine (an NNRTI), as a complete regimen to replace the current antiretroviral regimen for the treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA < 50 copies/mL).

## Results and Interpretation

### Included Studies

The evidence for this review was drawn from two identical phase III randomized (1:1), multi-centre, open-label, active-controlled, parallel-group, noninferiority (NI) trials (SWORD-1, n = 510; SWORD-2, n = 518). The first 48 weeks, known as the “early-switch” phase, was the basis for seeking market authorization. The remaining 52 to 148 weeks (late-switch phase) were non-comparative in design and constituted a long-term extension intended to support the findings from the early-switch phase and provide some evidence of treatment durability. Patients, who were virologically suppressed (HIV-1 RNA < 50 copies/mL) at baseline, were randomly assigned to switch to a dual antiretroviral (ARV) regimen of dolutegravir 50 mg plus rilpivirine 5 mg taken once daily or to continue their current triple antiretroviral therapy regimen (cAR) for 48 weeks. Of note, the trials did not employ the co-formulation of dolutegravir/rilpivirine; however, bioequivalence of the co-formulation compared with the individually administered drugs has been demonstrated (Appendix 5). The primary efficacy outcome in both trials was the proportion of patients with plasma HIV-1 RNA below 50 copies/mL at week 48 using the snapshot algorithm for the intention-to-treat exposed (ITT-E) population. The pre-specified NI margin for the primary outcome was -10% in both trials. The NI margin was selected prior to the FDA updating its (non-binding) guidance for industry on developing ARV drugs to treat HIV-1 infection, in which a stringent NI margin of 4% for “switch” NI trials was added based on virologic failure or loss.<sup>8</sup>

The two SWORD trials each enrolled patients with HIV-1 infection who were at least 18 years of age and who were treated without interruption for at least six months on a triple-drug ARV regimen composed of a backbone of two NRTIs plus either a NNRTI, an INSTI, or a boosted PI. At least two documented plasma HIV-1 RNA measurements below 50 copies/mL were required in the 12 months prior to screening to demonstrate virologic suppression on current triple-ARV therapy. If a previously suppressed plasma HIV-1 RNA rose above 50 copies/mL at any time within the six months prior to screening or two or more times within six to 12 months prior to screening, the patient was excluded. A switch in prior ARV therapy that occurred prior to study entry was permitted, but it could not have been due to virologic failure. Patients with hepatitis B infection or requiring treatment for hepatitis C (HCV) coinfection were ineligible to participate in either trial.

The primary efficacy outcome in both SWORD trials was the proportion of patients with plasma HIV-1 RNA below 50 copies/mL at week 48 using the snapshot algorithm for the ITT-E population. Secondary outcomes included the change from baseline in CD4+ lymphocyte count at week 24 and 48 and the proportion of patients with plasma HIV-1 RNA below 50 copies/mL at week 24. A pre-specified subgroup analysis by baseline third-agent class was also performed on the primary efficacy outcome and on the change from baseline in CD4+ lymphocyte count at week 48. A pre-planned analysis of the proportion of patients who were classified as snapshot virologic failures at week 48 was performed. Harms outcomes included the monitoring and recording of all adverse events and serious adverse events.

The major limitation of the SWORD trials was the selection of the NI margin. Updated industry guidance issued by the FDA<sup>8</sup> (after the SWORD protocol was apparently finalized) established a new stringent NI margin of 4% specifically intended for NI switch trials. Because patients in NI switch trials begin from a point of virologic suppression (< 50 copies/mL), the more salient outcome, in the FDA's point of view, is the loss of virologic suppression ( $\geq 50$  copies/mL) that could occur as a result of switching from a stable, virologically suppressive regimen to another regimen. The SWORD trials, whose patients were virologically suppressed to fewer than 50 copies/mL at baseline, used a traditional NI margin of  $-10\%$ , which was premised on achieving virologic suppression (not on minimizing loss of virologic control). This approach was consistent with past, undifferentiated FDA guidance for NI trials, but not with the FDA's updated guidance for NI switch trials. Although the investigators attempted to address the new FDA guidance by conducting a week 48 pre-planned (prior to data freeze) analysis of the proportion of "virologic failures," the fact remains that the original SWORD trials were not designed to evaluate NI based on a primary efficacy outcome of loss of virologic suppression ( $\geq 50$  copies/mL). Moreover, there were no statistical adjustments made to minimize the risk of a type I error from multiple outcome testing of secondary outcomes.<sup>9</sup> The CADTH Common Drug Review (CDR) team also noted that approximately 5% of patients in each group had no virologic data at week 48.

## Efficacy

In both SWORD-1 and SWORD-2, the proportion of patients with virologic failure (defined in Table 1) at week 48 was low in all groups in both trials. A pre-planned analysis of the pooled data showed that a similar proportion of patients taking dolutegravir plus rilpivirine (< 1%) compared with cAR (1%) were classified as virologic failures at week 48 (difference:  $-0.5\%$ ; 95% confidence interval [CI],  $-1.4\%$  to  $0.5\%$ ). Although the upper bound of the 95% CI was less than the 4% NI margin recommended by the FDA, the analysis was not controlled for multiplicity, complicating the interpretation of these findings.

In the primary (ITT-E) efficacy analysis of the proportion of patients with HIV-1 RNA below 50 copies/mL at 48 weeks, both SWORD trials produced similar results between dolutegravir plus rilpivirine and cAR groups (SWORD-1: 95% versus 96% and SWORD-2: 94% versus 94%, respectively) with a pooled difference of  $-0.2\%$  (95% CI,  $-3.0\%$  to  $2.5\%$ ). The secondary per-protocol analysis supported the findings from the primary analysis. In each trial, the pre-specified NI margin of  $-10\%$ , which was reduced to  $-8\%$  for the pooled analysis, was met (Table 1).

Two patients taking dolutegravir plus rilpivirine developed resistance-associated mutations (RAMs), but these did not affect susceptibility to treatment. Limited data from the late-switch



(single-arm extension) phase provided some supportive evidence for maintenance of long-term virologic suppression and low rates of virologic non-response (up to week 100).

## Harms

The overall frequency of adverse events was slightly higher in the dolutegravir plus rilpivirine group compared with the cAR group for both SWORD-1 (79% versus 74%) and SWORD-2 (75% versus 68%). This was not unexpected, given that the cAR group began the trial with at least six months of prior exposure to an ARV treatment regimen, unlike the (experimental) dolutegravir plus rilpivirine group. Nonetheless, the frequency of individual adverse events was similar between groups in each trial. The overall frequency of serious adverse events was similar between the dolutegravir plus rilpivirine and cAR groups (pooled: 5% versus 4%), while withdrawals due to adverse events were slightly higher in the dolutegravir plus rilpivirine group (pooled: 4% versus < 1%). Two deaths were recorded: one in SWORD-1 (cAR group: malignant neoplasm of the lung) and one in SWORD-2 (dolutegravir plus rilpivirine group: Kaposi sarcoma). Notable harms identified by patient groups and through discussion with the clinical expert consulted for this review included bone-related (i.e., fracture incidence, changes in bone mineral density [BMD]) and renal-related (i.e., various indicators of renal function and structure) harms (Table 1). Bone-related harms (changes in BMD but not fracture incidence) were specifically addressed in the DEXA substudy (Appendix 7) and showed small but clinically unimportant increases in areal density of the hip and lumbar spine with dolutegravir plus rilpivirine treatment compared with tenofovir disoproxil fumarate–based cAR. There was no indication of an adverse impact on renal function or structure from short-term (i.e., 48 weeks) exposure to dolutegravir plus rilpivirine treatment.

## Conclusions

In two phase III NI randomized controlled trials, patients who were switched from a stable, virologically suppressive (HIV-1 RNA < 50 copies/mL) triple-ARV regimen to a dual-therapy ARV regimen of dolutegravir plus rilpivirine maintained similar rates of viral load suppression (approximately 95%) after 48 weeks of treatment as the patients who remained on their stable, virologically suppressive triple-therapy ARV regimen. Virologic failure rates were low ( $\leq 2\%$ ) in both groups in both trials after 48 weeks of treatment. Other efficacy outcomes were generally supportive of the primary efficacy outcome. Harms were similar between groups after 48 weeks of treatment, except for a slightly higher proportion of withdrawals due to adverse events in the dolutegravir plus rilpivirine group. Bone-related harms, which were of specific interest to patients, and renal-related harms were both unremarkable.

A key limitation of the evidence was the use of an outdated NI margin, which is no longer consistent with current (non-binding) FDA guidance<sup>8</sup> for industry on ARV drug development in HIV infection. Although an attempt was made by the investigators to address the new FDA guidelines by conducting a pre-planned (prior to data freeze) analysis on the proportion of patients classified as “virologic failures,” the fact remains that the original SWORD trials were not designed to specifically evaluate the NI of treatments on the outcome of virologic loss (proportion of patients with HIV-1 RNA  $\geq 50$  copies/mL); the testing of this outcome was not controlled for multiplicity. Consequently, it is not possible to conclude whether NI was demonstrated statistically in the SWORD trials on the basis of the new FDA guidance. Nonetheless, the low rates of virologic failure observed, along with the high rates of virologic suppression maintained, suggest that dual therapy is a viable

therapeutic option for simplifying the ARV regimen in adult patients previously stabilized on a virologically suppressive triple-ARV regimen. This step-down approach is consistent with guidelines issued by the DHHS.<sup>1</sup>

**Table 1: Summary of Results**

Outcome	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
<b>Virologic failure<sup>a</sup></b>						
N (%), ITT-E	2 (< 1)	2 (< 1)	1 (< 1)	4 (2)	3 (< 1)	6 (1)
Adjusted difference in proportion, % (CI) <sup>b</sup>	0.0 (-1.3 to 1.4)		-1.0 (-2.4 to 0.5)		-0.5 (-1.4 to 0.5)	
Virologic failures included any of the following:						
• data in window not < 50 copies/mL	0	1 (< 1)	0	1 (< 1)	0	2 (< 1)
• discontinued for lack of efficacy	2 (< 1)	0	0	2 (< 1)	2 (< 1)	2 (< 1)
• discontinued for other reason while not < 50 copies/mL	0	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)
• change in ART	0	0	0	1 (< 1)	0	1 (< 1)
<b>HIV-1 RNA &lt; 50 copies/mL at week 48, ITT-E</b>						
N (%)	240 (95)	245 (96)	246 (94)	240 (94)	486 (95)	485 (95)
Adjusted difference in proportion, % (CI) <sup>c</sup>	-0.6 (-4.3 to 3.0)		0.2 (-3.9 to 4.2)		-0.2 (-3.0 to 2.5)	
<b>HIV-1 RNA &lt; 50 copies/mL at week 48, PP</b>						
N (%)	217 (96)	218 (96)	220 (95)	217 (96)	437 (96)	435 (96)
Adjusted difference in proportion, % (CI) <sup>c</sup>	-0.6 (-4.1 to 2.9)		-0.4 (-4.3 to 3.5)		-0.5 (-3.1 to 2.1)	
<b>Withdrawals</b>						
Total, N (%)	15 (6)	18 (7)	17 (6)	17 (6)	32 (6)	35 (7)
<b>SAEs</b>						
n, N (%)	9 (4)	12 (5)	18 (7)	9 (4)	27 (5)	21 (4)
<b>WDAEs</b>						
n, N (%)	9 (4)	2 (< 1)	12 (5)	1 (< 1)	21 (4)	3 (< 1)
<b>Notable harms(s)</b>						
<b>Serum creatinine (µmol/L)</b>						
N	238	243	245	241	483	484
Baseline, mean (SD)	78.4 (15.5)	78.2 (13.9)	76.4 (14.5)	77.8 (15.4)	77.4 (15.0)	78.0 (14.7)
Change from baseline to week 48, mean (SD)	7.6 (9.5)	0.9 (7.8)	8.8 (9.3)	-0.3 (7.5)	8.2 (9.4)	0.3 (7.7)
<b>eGFR (mL/min/1.73 m<sup>2</sup>)<sup>d</sup></b>						
N	238	243	245	241	483	484
Baseline, mean (SD)	100.0 (18.2)	100.7 (16.3)	101.4 (16.4)	100.1 (15.5)	100.7 (17.3)	100.4 (15.9)

Outcome		SWORD-1		SWORD-2		Pooled	
		DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
<b>Change from baseline to week 48, mean (SD)</b>		-8.3 (10.3)	-1.4 (7.9)	-10.0 (9.9)	-0.2 (7.9)	-9.2 (10.1)	-0.8 (7.9)
<b>Urine albumin to creatinine ratio (mg/mmol)</b>							
<b>N</b>	<b>Baseline</b>	218	223	227	226	445	449
	<b>Week 48</b>	166	171	178	181	344	352
<b>Baseline, median (range)</b>		0.60 (0.2 to 69.3)	0.70 (0.2 to 484.8)	0.60 (0.1 to 83.3)	0.60 (0.2 to 127.2)	0.60 (0.1 to 83.3)	0.60 (0.2 to 484.8)
<b>Change from baseline to week 48, median (range)</b>		-0.10 (-22.7 to 2.6)	-0.10 (-366.7 to 12.6)	-0.15 (-57.1 to 13.3)	0.00 (-126.7 to 13.0)	-0.10 (-57.1 to 13.3)	-0.05 (-366.7 to 13.0)
<b>Urine protein to creatinine ratio (mg/mmol)</b>							
<b>N</b>	<b>Baseline</b>	223	219	230	224	453	443
	<b>Week 48</b>	176	182	192	193	368	375
<b>Baseline, median (range)</b>		8.70 (2.0 to 185.8)	9.20 (2.6 to 701.5)	8.60 (3.4 to 180.2)	8.10 (3.1 to 148.5)	8.60 (2.0 to 185.8)	8.60 (2.6 to 701.5)
<b>Change from baseline to week 48, median (range)</b>		-1.90 (-175.6 to 7.7)	0.45 (-554.6 to 117.2)	-1.40 (-152.9 to 23.4)	0.30 (-15.1 to 28.1)	-1.60 (-175.6 to 23.4)	0.40 (-554.6 to 117.2)
<b>Urine glucose (dipstick)</b>							
Negative at baseline, n (%)		NR	NR	NR	NR	NR	NR
Negative at week 48, n (%)		225 (> 99)	229 (99)	235 (98)	235 (> 99)	460 (99)	464 (> 99)
<b>Bone-related</b>		Refer to supplemental issue — “DEXA substudy”					

AE = adverse event; ART = antiretroviral therapy; cAR = current antiretroviral regimen; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; CVW = confirmed virologic withdrawal; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; INSTI = integrase strand transfer inhibitor; IQR = interquartile range; ITT-E = intention-to-treat exposed; NNRTI = non-nucleoside reverse transcriptase inhibitor; NR = not reported; PI = protease inhibitor; PP = per-protocol; PVW = precautionary virologic withdrawal; RNA = ribonucleic acid; RPV = rilpivirine; SAE = serious adverse event; SD = standard deviation; SE = standard error; VAS = visual analogue scale; WDAE = withdrawal due to adverse event.

<sup>a</sup> Pre-planned analysis.

<sup>b</sup> Based on CMH stratified analysis adjusting for age (< 50, ≥ 50 years old) and baseline third-agent class (PI, NNRTI, INSTI).

<sup>c</sup> Difference: Proportion on (DTG + RPV) minus proportion on cAR; based on CMH stratified analysis adjusting for age (< versus ≥ 50 years old) and baseline third agent (PI, NNRTI, INSTI).

<sup>d</sup> Employing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Source: SWORD-1 Clinical Study Report,<sup>10</sup> SWORD-2 Clinical Study Report.<sup>11</sup>

## Introduction

### Disease Prevalence and Incidence

HIV is the virus responsible for causing HIV infection.<sup>12</sup> Of the two subtypes of the virus — HIV-1 and HIV-2 — HIV-1 is the most prevalent globally, and is often simply referred to as HIV.<sup>12</sup> Transmission of HIV occurs via body fluids such as blood, semen, genital secretions, and breast milk, most often from unprotected sexual intercourse or through sharing of contaminated needles and syringes.<sup>13</sup> Mother-to-child transmission can also occur during pregnancy, birth, or breast-feeding.<sup>13</sup> By attacking the CD4+ and T-cells of the body's immune system, HIV infection renders the body unable to mount an adequate immune response to defend itself against opportunistic pathogens and certain cancers.<sup>12,14</sup> Left untreated, HIV infection can progress to acquired immunodeficiency syndrome (AIDS) and, ultimately, death.<sup>14</sup> Fortunately, since the availability of highly active antiretroviral therapy (HAART) in the mid-1990s, HIV infection has evolved from a high-fatality illness to a chronic disease with which patients are able to enjoy long, productive lives by keeping viral loads in check with HAART.<sup>14</sup> According to the patient input received, despite the great strides in survival and quality of life from HIV treatment, there remains a stigma attached to the disease.

Surveillance data from the Public Health Agency of Canada report that the national rate of HIV diagnosis (all ages) in Canada in 2014 was 5.8 per 100,000 population, with the highest diagnosis rates found in Saskatchewan (10.8), Yukon (8.2), and Alberta (6.7).<sup>15</sup> It is estimated that about one in five people infected with HIV are undiagnosed in Canada.<sup>16</sup> In 2014, close to one-third of HIV cases were diagnosed in the 30 to 39 age group, which accounted for the largest proportion of cases; this was followed by the 40 to 49 age group (22.8%).<sup>15</sup> At the end of 2014, there were between 54,000 and 76,000 Canadians living with HIV infection.<sup>16</sup> Females accounted for about one-quarter of HIV cases.<sup>15</sup> When exposure was known, the most common exposure category was “men who have sex with men” (48.8%), followed by heterosexual contact (29.2%), and injection drug use (13.1%).<sup>15</sup>

### Standards of Therapy

Triple antiretroviral (ARV) therapy, consisting of a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) anchored by a third agent from either the non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI) class is the current standard of care for the initial treatment of HIV-1 infection.<sup>1</sup> The primary goal of ARV therapy is to suppress HIV-1 ribonucleic acid (RNA) below detectable limits (< 50 copies/mL). Other goals of therapy follow from maximal viral load suppression and include restoration and improvement of immune function; enhanced quality and quantity of life-years; and reduced risks of HIV-related complications, virus transmission, and death.<sup>1</sup> ARV therapy is a lifelong commitment, requiring high levels of sustained treatment adherence. To simplify medication-taking and support long-term adherence, six single-tablet regimens (STRs) have been developed and marketed,<sup>2,3</sup> alongside other non-STRs,<sup>1</sup> providing clinicians and patients with an array of therapeutic options from which to choose. While there is no therapeutic need that is unmet by current ARV therapies according to the clinical expert consulted for this review, there has been some interest in simplifying or stepping down ARV regimens once maximal viral load suppression has been achieved.<sup>4,5</sup> Reasons for this include improving convenience (e.g., no requirement for co-administration with food, reduced pill burden), preventing drug–drug

interactions, improving tolerability and minimizing exposure to treatment-related toxicity, and reducing treatment cost.<sup>1,5</sup> This has given rise to the step-down concept, in which a patient on a maximally effective, virologically suppressive, stable triple-ARV regimen is switched to a more simplified (e.g., dual) ARV regimen.<sup>5,6</sup> According to the *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living With HIV* issued by the US Department of Health and Human Services (DHHS),<sup>1</sup> maintaining virologic suppression without compromising future treatment options is of the utmost importance when considering a switch from a virologically suppressive ARV regimen to another, more simplified ARV regimen. For switching to a two-drug regimen, the DHHS guidelines include two regimen options that it considers to have good supporting evidence: a boosted PI plus emtricitabine (FTC) or lamivudine (3TC), or dolutegravir (DTG) plus rilpivirine (RPV).<sup>1</sup> Switching to a monotherapy regimen is not recommended due to a lack of efficacy and development of treatment resistance.<sup>1</sup>

## Drug

Juluca (DTG 50 mg/RPV 25 mg) is an oral single-tablet regimen indicated for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL). Reimbursement is being sought by the manufacturer in accordance with the indication.

Juluca consists of an INSTI and a NNRTI. DTG, an INSTI, “inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid integration, which is essential to the HIV replication cycle.”<sup>17</sup> The activity of rilpivirine, an NNRTI, is “mediated by the non-competitive inhibition of HIV-1 reverse transcriptase.”<sup>17</sup>

The objective of this systematic review was to evaluate the beneficial and harmful effects of Juluca for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL).

Key characteristics of common triple-ARV regimens are presented in Table 2.

**Table 2: Key Characteristics of Common Triple Antiretroviral Therapy Regimens<sup>a</sup>**

Comparator Regimens	Brand	Dosage Strengths	Indications <sup>b</sup>	Key Side Effects / Safety Issues
<b>Comparator regimens included in cost-utility analysis submitted by manufacturer</b>				
DRV/c + TAF/FTC	Prezcobix <sup>c</sup>	<b>DRV/c:</b> 800 mg/150 mg	In combination with other ARV drugs for the treatment of HIV infection in treatment-naïve and treatment-experienced patients without DRV RAMs <sup>18</sup>	<b>DRV:</b> diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., P–R interval prolongation) <sup>14,19</sup> <b>c:</b> can falsely increase SCr <sup>19</sup>
	Descovy	<b>TAF/FTC:</b> 10 mg/200 mg 25 mg/200 mg	In combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg) <sup>21</sup>	<b>TAF:</b> similar to TDF, but may have less renal and bone toxicity <sup>20</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup>
DTG/ABC/3TC	Triumeq	<b>DTG:</b> 50 mg	Treatment of HIV-1 infection in adults and adolescents aged ≥ 12 years and weighing ≥ 40 kg <sup>22</sup>	<b>DTG:</b> insomnia, headache, depression; early benign increase in SCr <sup>14,19</sup> <b>ABC:</b> risk of severe hypersensitivity reaction in genetically susceptible patients; possible increased risk for MI <sup>14,19</sup> <b>3TC:</b> generally well tolerated <sup>14</sup>
		<b>ABC:</b> 600 mg		
		<b>3TC:</b> 300 mg		
DTG + TAF/FTC	Tivicay	<b>DTG:</b> 50 mg	Treatment of HIV-1 infection in adults and in INSTI-naïve children weighing ≥ 30 kg <sup>23</sup>	<b>DTG:</b> insomnia, headache, depression; early benign increase in SCr <sup>14,19</sup> <b>TAF:</b> Similar to TDF, but may have less renal and bone toxicity <sup>20</sup>
		Descovy		
EVG/c/TAF/FTC	Genvoya <sup>c</sup>	<b>EVG:</b> 150 mg	A complete regimen for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg) and with no known RAMs to the individual components of Genvoya <sup>24</sup>	<b>EVG:</b> nausea, diarrhea, insomnia, headache, depression; early benign increase in SCr <sup>1,14,19</sup> <b>c:</b> can falsely increase SCr <sup>19</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup> <b>TAF:</b> Similar to TDF, but may have less renal and bone toxicity <sup>20</sup>
		<b>c:</b> 150 mg		
		<b>FTC:</b> 200 mg		
		<b>TAF:</b> 10 mg		
RPV/TAF/FTC	Odefsey <sup>c</sup>	<b>RPV:</b> 25 mg	A complete regimen for the treatment of adults infected with HIV-1 with no known RAMs to the NNRTI class, tenofovir, or FTC, and with a VL ≤ 100,000 copies/mL <sup>25</sup>	<b>RPV:</b> depression, insomnia, rash, headache; early benign increase in SCr <sup>14</sup> <b>TAF:</b> similar to TDF, but may have less renal and bone toxicity <sup>20</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup>
		<b>TAF:</b> 25 mg		
		<b>FTC:</b> 200 mg		

Comparator Regimens	Brand	Dosage Strengths	Indications <sup>b</sup>	Key Side Effects / Safety Issues
<b>Additional relevant comparator regimens</b>				
DRV/c + TDF/FTC	Prezcobix <sup>c</sup>	<b>DRV/c:</b> 800 mg/150 mg	In combination with other ARV drugs for the treatment of HIV infection in treatment-naive and in treatment-experienced patients without DRV RAMs <sup>18</sup>	<b>DRV:</b> diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., P–R interval prolongation) <sup>14,19</sup> <b>c:</b> can falsely increase SCr <sup>19</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>14</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup>
	Truvada, generics	<b>TDF:</b> 300 mg <b>FTC:</b> 200 mg	In combination with other ARV drugs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults <sup>26</sup>	<b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>14</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup>
DRV+ r + TDF/FTC	Prezista <sup>c</sup>	<b>DRV:</b> 800 mg	Co-administered with 100 mg ritonavir and with other ARV drugs for the treatment of HIV-1 infection <sup>27</sup>	<b>DRV:</b> diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., P–R interval prolongation) <sup>14,19</sup>
	Norvir <sup>c</sup>	<b>r:</b> 100 mg	In combination with other ARV drugs for the treatment of HIV infection when therapy is warranted <sup>28</sup>	<b>r:</b> diarrhea, nausea, headache, paresthesia, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., P–R interval prolongation) <sup>14,19</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>19</sup>
	Truvada, generics	<b>TDF:</b> 300 mg <b>FTC:</b> 200 mg	In combination with other ARV drugs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults <sup>26</sup>	<b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup>
DTG + TDF/FTC	Tivicay	<b>DTG:</b> 50 mg	Treatment of HIV-1 infection in adults and in INSTI-naive children weighing ≥ 30 kg <sup>23</sup>	<b>DTG:</b> insomnia, headache, depression; early benign increase in SCr <sup>14,19</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>14</sup>
	Truvada, generics	<b>TDF:</b> 300 mg <b>FTC:</b> 200 mg	In combination with other ARV drugs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults <sup>26</sup>	<b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup>
EVG/c/TDF/FTC	Stribild <sup>c</sup>	<b>EVG:</b> 150 mg	A complete regimen for the treatment of adults aged ≥ 18 years infected with HIV-1 with no known mutations to the INSTI class, tenofovir, or FTC <sup>29</sup>	<b>EVG:</b> nausea, diarrhea, insomnia, headache, depression; early benign increase in SCr <sup>1,14,19</sup> <b>c:</b> can falsely increase SCr <sup>19</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>14</sup>
		<b>c:</b> 150 mg		
		<b>FTC:</b> 200 mg		
		<b>TDF:</b> 300 mg		



Comparator Regimens	Brand	Dosage Strengths	Indications <sup>b</sup>	Key Side Effects / Safety Issues
RPV/TDF/FTC	Complera <sup>c</sup>	<b>RPV:</b> 25 mg <b>TDF:</b> 300 mg <b>FTC:</b> 200 mg	A complete regimen for the treatment of adults infected with HIV-1 with no known RAMs to the NNRTI class, tenofovir, or FTC, and with a VL ≤ 100,000 copies/mL <sup>30</sup>	<b>RPV:</b> depression, insomnia, rash, headache; early benign increase in SCr <sup>14</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>14</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup>
EFV/TDF/FTC	Atripla <sup>d</sup>	<b>EFV:</b> 600 mg <b>TDF:</b> 300 mg <b>FTC:</b> 200 mg	For use alone as a complete regimen or in combination with other ARV drugs for the treatment of HIV-1 infection in adults <sup>31</sup>	<b>EFV:</b> insomnia, vivid dreams, depressed mood, dizziness, headache, rash. Avoid in patients with history of anxiety, depression, or psychosis. Contraindicated in first trimester of pregnancy <sup>14,19</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>14</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>19</sup>

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMD = bone mineral density; c = cobicistat; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; r = low-dose ritonavir; RAM = resistance-associated mutation; RPV = rilpivirine; SCr = serum creatinine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; VL = viral load.

<sup>a</sup> All regimens are administered orally once daily.<sup>1</sup>

<sup>b</sup> Health Canada indication.

<sup>c</sup> Must be taken with food or a meal.<sup>1</sup>

<sup>d</sup> Must be taken on an empty stomach.<sup>1</sup>

Source: Product monographs for the following: Prezcoibix,<sup>18</sup> Tivicay,<sup>23</sup> Descovy,<sup>21</sup> Genvoya,<sup>24</sup> Odefsey,<sup>25</sup> Triumeq,<sup>22</sup> Truvada,<sup>26</sup> Prezista,<sup>27</sup> Norvir,<sup>28</sup> Stribild,<sup>29</sup> Complera,<sup>30</sup> and Atripla;<sup>31</sup> e-CPS;<sup>14</sup> RxFiles;<sup>19</sup> and AIDSinfo.<sup>1</sup>



## Objectives and Methods

### Objectives

To perform a systematic review of the beneficial and harmful effects of the fixed-dose co-formulation of DTG 50 mg plus RPV 25 mg for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL).

### Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

**Table 3: Inclusion Criteria for the Systematic Review**

<b>Patient Population</b>	Adults ≥ 18 years of age with HIV-1 infection who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) Subgroups: <ul style="list-style-type: none"> <li>• Baseline VL prior to suppressive triple-ARV regimen</li> <li>• Baseline CD4+ prior to suppressive triple-ARV regimen</li> <li>• Biological sex</li> <li>• Baseline ARV regimen (e.g., based on third-agent class [i.e., INSTI, NNRTI, or boosted PI] added to 2 NRTIs)</li> </ul>
<b>Intervention</b>	DTG 50 mg plus RPV 25 mg once daily, in fixed-dose co-formulation
<b>Comparators</b>	Standard care triple-ARV regimen: either 2 NRTIs + 1 INSTI; 2 NRTIs + 1 NNRTI; or 2 NRTIs + 1 PI (boosted with ritonavir or cobicistat)
<b>Outcomes</b>	<p><b>Key efficacy outcomes:</b></p> <ul style="list-style-type: none"> <li>• % of patients with HIV-1 RNA VL ≥ 50 copies/mL at 48 weeks</li> <li>• % of patients with HIV-1 RNA VL &lt; 50 copies/mL at 48 weeks</li> </ul> <p><b>Other efficacy outcomes:</b></p> <ul style="list-style-type: none"> <li>• CD4+ count</li> <li>• Development of drug resistance</li> <li>• HRQoL</li> <li>• adherence to ARV regimen</li> </ul> <p><b>Harms outcomes:</b></p> <ul style="list-style-type: none"> <li>• mortality</li> <li>• SAEs</li> <li>• WDAEs</li> <li>• AEs (e.g., bone-related<sup>a</sup> [fractures, BMD], renal function)</li> </ul>
<b>Study Design</b>	Published and unpublished RCTs, phase III and higher

AE = adverse event; ARV = antiretroviral; BMD = bone mineral density; DTG = dolutegravir; HRQoL = health-related quality of life; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RCT = randomized controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; SAE = serious adverse event; VL = viral load; WDAE = withdrawal due to adverse events.

<sup>a</sup> In the input received by CADTH from patient groups, these outcomes were identified as being of particular importance to patients.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were Juluca, RPV, and DTG.

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 24, 2018. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on September 20, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Databases; and an Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

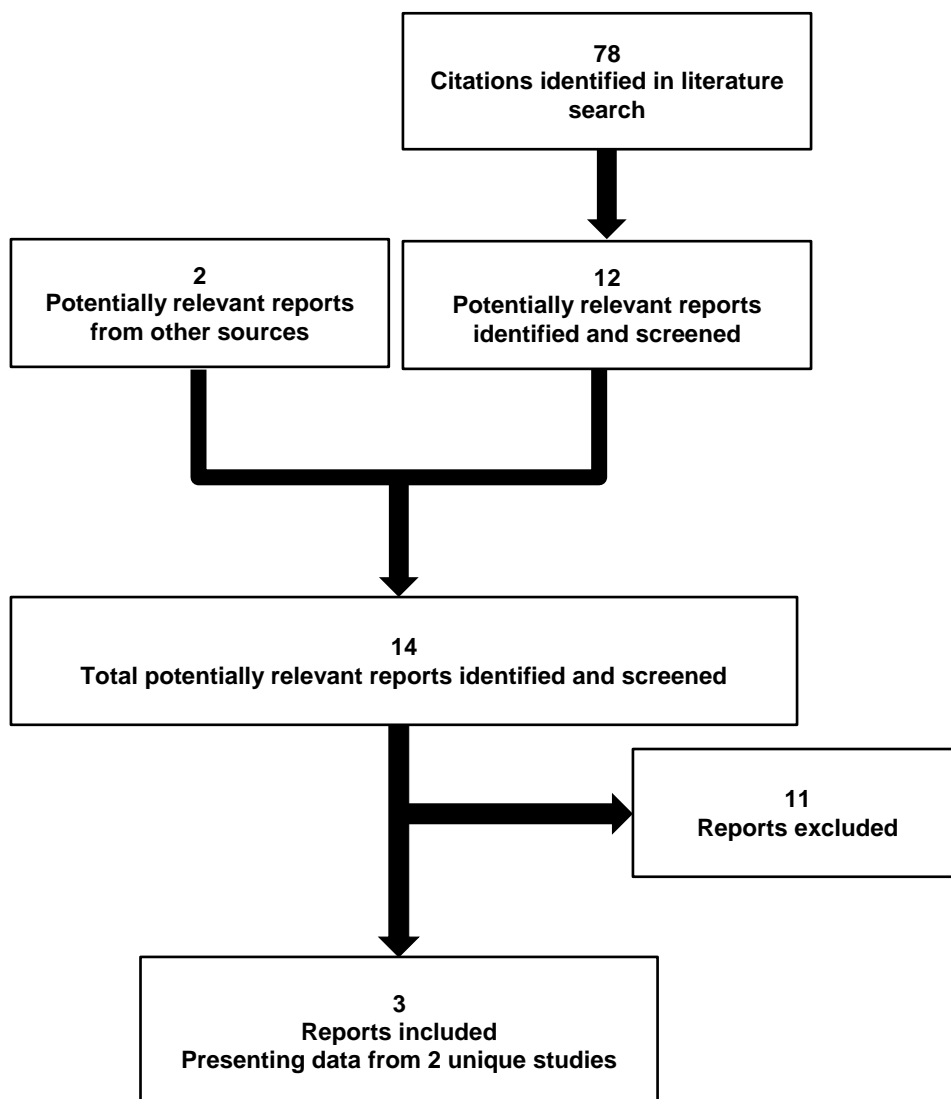
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

## Results

### Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

**Figure 1: Flow Diagram for Inclusion and Exclusion of Studies**



**Table 4: Details of Included Studies**

		SWORD-1	SWORD-2
DESIGNS & POPULATIONS	<b>Study Design</b>	Phase III, randomized (1:1), multi-centre, open-label, active-controlled, parallel-group, noninferiority trial. Stratification factors: baseline third-agent class; age (< or ≥ 50 years); planned participation in the DEXA substudy	
	<b>Locations</b>	SWORD-1: 66 centres in 13 countries; SWORD-2: 60 centres in 11 countries. Argentina, Australia, Belgium, <sup>a</sup> Canada, France, Germany, Italy, Netherlands, <sup>a</sup> Russia, Spain, Taiwan, UK, US	
	<b>Randomized (N)</b>	510	518
	<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• HIV-1 infected non-pregnant adults ≥ 18 years of age</li> <li>• Uninterrupted current ARV therapy (either first or second regimen<sup>b</sup>) for ≥ 6 months prior to screening consisting of 2 NRTIs plus either an INSTI, NNTI, or a boosted PI</li> <li>• Documented evidence of ≥ 2 plasma HIV-1 RNA measurements &lt; 50 copies/mL in the 12 months prior to screening</li> <li>• Plasma HIV-1 RNA &lt; 50 copies/mL at screening</li> </ul>	
	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Plasma HIV-1 RNA ≥ 50 copies/mL (after confirmed suppression &lt; 50 copies/mL): either a single measurement within 6 months prior to screening or ≥ 2 measurements within 6 to 12 months prior to screening</li> <li>• Any switch to a second-line regimen due to virologic failure (defined as a confirmed plasma HIV-1 RNA ≥ 400 copies/mL after initial suppression to &lt; 50 copies/mL while on first-line ARV regimen)</li> <li>• Evidence of viral resistance based on the presence of any resistance-associated major PI, INSTI, NRTI, or NNRTI mutation</li> <li>• Any degree of hepatic impairment</li> <li>• Positivity for HBV surface antigen or with an anticipated need for HCV therapy during the study</li> </ul>	
DRUGS	<b>Intervention</b>	DTG 50 mg + RPV 25 mg orally once daily	
	<b>Comparator(s)</b>	Current ARV regimen: 2 NRTIs plus either an INSTI, an NNRTI, or a PI	
DURATION	<b>Phase</b>		
	Run-in	≤ 4 weeks	
	Double-blind	48 weeks (early switch)	
	Single-arm extension	52 to 148 weeks (late switch)	
OUTCOMES	<b>Primary End Point</b>	Proportion of patients with plasma HIV-1 RNA < 50 copies/mL at week 48 using the snapshot algorithm for the ITT-E population	
	<b>Other End Points</b>	<p><i>Secondary efficacy:</i></p> <ul style="list-style-type: none"> <li>• change from baseline in CD4+ lymphocyte count at week 24 and 48</li> <li>• proportion of patients with plasma HIV RNA &lt; 50 copies/mL at week 24 using the snapshot algorithm for the ITT-E population</li> <li>• subgroup analyses by baseline third-agent class: <ul style="list-style-type: none"> <li>○ proportion of patients with HIV-1 RNA &lt; 50 copies/mL at week 48 using the snapshot algorithm for the ITT-E population</li> <li>○ changes from baseline in CD4+ lymphocyte counts at week 48</li> </ul> </li> </ul> <p><i>Exploratory efficacy:</i></p> <ul style="list-style-type: none"> <li>• by patient subgroups (e.g., age, biological sex, baseline CD4+) <ul style="list-style-type: none"> <li>○ proportion of patients with HIV-1 RNA &lt; 50 copies/mL at week 48 using the snapshot algorithm for the ITT-E population</li> <li>○ changes from baseline in CD4+ lymphocyte counts at week 48</li> </ul> </li> </ul> <p><i>Additional analyses of efficacy; pre-planned prior to data freeze:</i></p> <ul style="list-style-type: none"> <li>• proportion of patients who were classified as snapshot virological failure at week 48</li> </ul>	

		SWORD-1	SWORD-2
		Safety outcomes included the monitoring and recording of all AEs and SAEs (e.g., laboratory, clinical; drug–drug interactions)	
<b>NOTES</b>	<b>Publications</b>	Clinical Study Report <sup>10</sup> Llibre et al., 2018 <sup>32</sup>	Clinical Study Report <sup>11</sup> Llibre et al., 2018 <sup>32</sup>

AE = adverse event; ARV = antiretroviral; copies/mL = copies per millilitre; DTG = dolutegravir; HBV = hepatitis B virus; HCV = hepatitis C virus; INSTI = integrase strand transfer inhibitor; ITT-E = intention-to-treat exposed; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RNA = ribonucleic acid; RPV = rilpivirine; SAE = serious adverse event.

Source: SWORD-1 Clinical Study Report,<sup>10</sup> SWORD-2 Clinical Study Report,<sup>11</sup> Llibre et al. (2018).<sup>32</sup>

<sup>a</sup> SWORD-1 only.

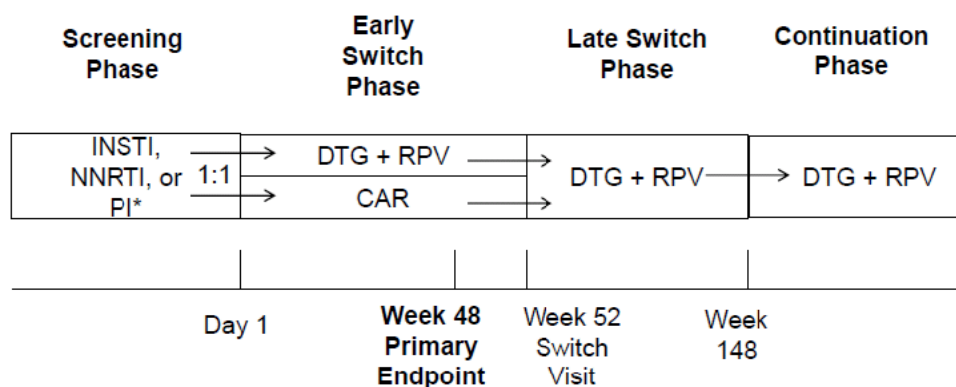
<sup>b</sup> Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability and/or safety concerns or access to medications, or convenience/simplification.

## Included Studies

### Description of Studies

SWORD-1 (n = 510; 13 countries) and SWORD-2 (n = 518; 11 countries) were a pair of identical phase III, randomized (1:1), multi-centre, open-label, active-controlled, parallel-group trials stratified by age (< or ≥ 50 years), baseline third-agent class (NNRTI, PI, INSTI), and planned participation in the DEXA substudy conducted in patients with HIV-1 infection. The primary objective of each trial was to test the noninferiority (NI) of switching from the patient’s current virologically suppressive (HIV-1 RNA < 50 copies/mL), stable three-drug antiretroviral (ARV) regimen to a two-drug ARV regimen consisting of DTG 50 mg plus RPV 25 mg. The primary outcome for each trial was the proportion of patients who achieved a plasma HIV-1 RNA < 50 copies/mL at week 48. The trials, which were designed for 148 weeks of follow-up covering “early” (week 0 to 48) and “late” (week 52 to 148) switch periods, are still ongoing. A schematic of the SWORD trials’ design is presented in Figure 2.

**Figure 2: Design of SWORD Trials**



CAR = current antiretroviral regimen; DTG = dolutegravir; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; RPV = rilpivirine; PI = protease inhibitor.

\* Plus 2NRTIs.

Source: SWORD-1 Clinical Study Report.<sup>10</sup>

## Populations

### *Inclusion and Exclusion Criteria*

The two SWORD trials each enrolled patients with HIV-1 infection who were at least 18 years of age and who were treated without interruption for at least six months on a triple-drug ARV regimen composed of a backbone of two NRTIs plus either a NNRTI, an INSTI, or a boosted PI. At least two documented plasma HIV-1 RNA measurements less than 50 copies/mL were required prior to screening to demonstrate virologic suppression on current triple-ARV therapy. If a previously suppressed plasma HIV-1 RNA rose above 50 copies/mL at any time within six months of screening or two or more times within six to 12 months of screening, the patient was excluded. Although a switch in prior ARV therapy was permitted, it could not have been due to virologic failure. Likewise, any evidence of resistance-associated mutations in any of the four ARV classes was grounds for exclusion. Patients with any degree of hepatic impairment were ineligible to participate in either trial, as were patients who tested positive for hepatitis B virus surface antigen at screening or with an anticipated need for hepatitis C virus (HCV) therapy during the study.

### *Baseline Characteristics*

Baseline characteristics (Table 5) were generally well balanced between the DTG plus RPV group and the current antiretroviral regimen (cAR) group in both SWORD trials. Patients had a mean age of approximately 44 years in SWORD-1 and 43 years in SWORD-2. In both trials, patients weighed approximately 76 kg, which corresponded to a mean body mass index (BMI) of 25 kg/m<sup>2</sup>, which is considered overweight.<sup>33</sup> Men made up 79% and 77% of trial participants in SWORD-1 and SWORD-2, respectively. There was more racial diversity in SWORD-1 than SWORD-2, where white, Asian, and black/African-American patients accounted for 76%, 12%, and 10% of participants in SWORD-1 compared with 84%, 6%, and 6% in SWORD-2. Within SWORD-1, there were slightly more white patients randomized to DTG plus RPV (79%) compared with cAR (73%). About 7% of patients in each trial were co-infected with, but not receiving treatment for, HCV. NRTI use was documented in all (100%) patients in each trial at screening while NNRTI, PI, and INSTI use was approximately 52%, 29%, and 19% in SWORD-1, and 56%, 23%, and 21% in SWORD-2. The most frequent ARV regimen at screening was co-formulated efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF), which was taken by 24% and 29% of patients in SWORD-1 and SWORD-2, respectively. Other ARV regimens taken by more than 5% of patients are presented in Table 5. Concomitant non-ARV medications taken by at least 10% of patients regardless of treatment assignment were similar between groups in SWORD-1 and included paracetamol (23%), ibuprofen (17%), amoxicillin (13%), and influenza vaccine (12%). In SWORD-2, a similar pattern of use emerged with paracetamol (19%), ibuprofen (12%), amoxicillin (14%), and the influenza vaccine (13%). Additionally, cholecalciferol (10%), and azithromycin (9%) were taken by at least 10% of patients in either group. In SWORD-2, there appeared to be slightly less use of influenza vaccine in the DTG plus RPV group (10%) compared with the cAR group (16%).

**Table 5: Summary of Baseline Characteristics (ITT-E Set)**

Baseline Characteristics		SWORD-1 (n = 508)		SWORD-2 (n = 516)	
		DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)
Age (years)	Mean (SD)	43.6 (10.9)	43.6 (10.8)	43.3 (11.3)	43.2 (9.6)
	Median (range)	43.0 (23 to 78)	43.0 (22 to 76)	43.0 (21 to 79)	43.0 (22 to 69)
Sex, n (%)	Male	194 (77)	205 (80)	199 (76)	198 (78)
	Female	58 (23)	51 (20)	62 (24)	57 (22)
Race, n (%)	White	198 (79)	188 (73)	223 (85)	210 (82)
	Asian	25 (10)	34 (13)	13 (5)	16 (6)
	Black/African-American	24 (10)	27 (11)	13 (5)	20 (8)
	Other	5 (2)	7 (3)	12 (5)	9 (4)
Weight (kg)	Mean (SD)	76.1 (15.5)	74.9 (16.0)	76.2 (13.9)	75.3 (13.6)
BMI (kg/m <sup>2</sup> )	Mean (SD)	25.5 (4.8)	25.2 (5.3)	25.6 (4.4)	25.3 (4.5)
Baseline HIV-1 RNA (copies/mL)	< 50 copies/mL	247 (98)	253 (99)	259 (99)	251 (98)
Baseline CD4+ (log <sub>10</sub> cells/mm <sup>3</sup> )	Median (range)	2.8 (1.5 to 3.2)	2.8 (2.0 to 3.2)	2.8 (2.1 to 3.3)	2.8 (2.0 to 3.2)
Hepatitis B and C test positivity	B only	0	1 (< 1)	0	1 (< 1)
	C only	15 (6)	19 (7)	13 (5)	21 (8)
	B and C	0	0	0	0
	Neither	237 (94)	236 (92)	247 (95)	233 (91)
ART at screening by drug class, n (%)	NRTI	252 (100)	256 (100)	261 (100)	255 (100)
	NNRTI	131 (52)	134 (52)	144 (55)	144 (56)
	PI	75 (30)	74 (29)	58 (22)	62 (24)
	INSTI	46 (18)	48 (19)	59 (23)	49 (19)
ART at screening by regimen (> 5% in either group), n (%)	EFV/FTC/TDF	60 (24)	64 (25)	70 (27)	78 (31)
	DRV/r + FTC/TDF	24 (10)	14 (5)	21 (8)	17 (7)
	ATV/r + FTC/TDF	19 (8)	21 (8)	≤ 5%	≤ 5%
	EVG/COBI/FTC/TDF	15 (6)	9 (4)	≤ 5%	≤ 5%
	RPV/FTC/TDF	16 (6)	15 (6)	13 (5)	19 (7)
	RAL + FTC/TDF	≤ 5%	≤ 5%	20 (8)	17 (7)
Concomitant non-ARV medication at screening (≥ 10% in either group), n (%)	Acetaminophen	52 (21)	63 (25)	51 (20)	47 (18)
	Ibuprofen	43 (17)	45 (18)	36 (14)	26 (10)
	Amoxicillin	30 (12)	34 (13)	34 (13)	37 (15)
	Influenza vaccine	28 (11)	34 (13)	27 (10)	41 (16)
	Cholecalciferol	< 10%	< 10%	29 (11)	23 (9)
	Azithromycin	< 10%	< 10%	27 (10)	20 (8)

ART = antiretroviral therapy; ATV/r = atazanavir boosted with ritonavir; BMI = body mass index; cAR = current antiretroviral regimen; copies/mL = copies per millilitre; COBI = cobicistat; DTG = dolutegravir; DRV/r = darunavir boosted with ritonavir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; ITT-E = intention-to-treat exposed; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RNA = ribonucleic acid; RPV = rilpivirine; SD = standard deviation; TDF = tenofovir disoproxil fumarate.

Source: SWORD-1 Clinical Study Report<sup>10</sup>, SWORD-2 Clinical Study Report.<sup>11</sup>

## Interventions

Patients were randomly assigned 1:1 to open-label regimens of either a dual-ARV regimen consisting of DTG 50 mg plus RPV 25 mg taken once daily, or continuation of their current triple-ARV regimen (cAR) for a total of 48 weeks (early-switch phase). Between 48 and 52 weeks, patients with confirmed virologic suppression who were originally assigned to continue their cAR during weeks 0 to 48 were switched over to DTG 50 mg plus RPV 25 mg once daily; thus, all patients in this late-switch phase were on the dual-ARV regimen from weeks 52 to 148.

## Outcomes

The primary efficacy outcome for both SWORD trials was the proportion of patients with plasma HIV-1 RNA below 50 copies/mL at week 48 using the snapshot algorithm for the intention-to-treat exposed (ITT-E) population. The snapshot algorithm is an analytic approach that reports on an outcome (e.g., proportion of patients with plasma HIV-1 RNA < 50 copies/mL) at a specific point in time (e.g., at week 48) in contrast to the more complex time to loss of virological response (TLOVR) analytic approach, which examines the pattern of change in an outcome over time (e.g., at each study visit).<sup>8</sup>

Secondary outcomes included the change from baseline in CD4+ lymphocyte count at weeks 24 and 48 and the proportion of patients with plasma HIV-1 RNA below 50 copies/mL at week 24 using the snapshot algorithm for the ITT-E population. A pre-specified subgroup analysis by baseline third-agent class was also performed on the primary efficacy outcome and on the change from baseline in CD4+ lymphocyte count at week 48.

Exploratory subgroup analyses by such factors as age, biological sex, and baseline CD4+ count were similarly conducted on the primary efficacy outcome and on the change from baseline in CD4+ lymphocyte count at week 48. In addition, a pre-planned analysis of the proportion of patients who were classified as snapshot virologic failures at week 48 was performed.<sup>9</sup> In the SWORD trials, virologic failure included patients whose viral load data were not below 50 copies/mL; who discontinued due to lack of efficacy; who discontinued for another reason while viral load was not below 50 copies/mL; or who had had a change in ARV therapy. The SWORD trial criteria for virologic failure are aligned with those in the FDA's updated guidance.<sup>8</sup>

Other exploratory outcomes included health-related quality of life (HRQoL) and a subjective rating of ARV regimen adherence. HRQoL was assessed using the EuroQoL 5-Dimensions 5-Levels questionnaire (EQ-5D-5L), a generic quality-of-life instrument that may be applied to a wide range of health conditions and treatments to capture the net effect of treatment benefits and harms.<sup>34</sup> The EQ-5D-5L consists of five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) rated on a scale of five levels (ranging from 1 ["no problems"] to 5 ["extreme problems" or "unable to perform"]).<sup>34</sup> The EQ-5D-5L also has a visual analogue scale (VAS), by which overall health is self-rated on a scale ranging from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine").<sup>34</sup> Subjective rating of adherence to the assigned ARV regimen was similarly assessed with a VAS, by which patients self-rated their perceived level of average adherence on a scale ranging from 0 ("no HIV medication") to 100 ("every dose of HIV medication"). Little background information was provided about the VAS used to assess subjective adherence.



Harms outcomes included the monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs) (e.g., laboratory, clinical; drug–drug interactions).

### Statistical Analysis

SWORD-1 and SWORD-2 were identically designed, NI “switch” trials, stratified by age (< or ≥ 50 years), baseline third-agent class (NNRTI, PI, INSTI), and planned participation in the DEXA substudy, which examined the NI of switching from a virologically suppressive (i.e., fewer than 50 copies/mL) current triple-therapy antiretroviral regimen (cAR) to a dual-therapy antiretroviral (ARV) regimen consisting of DTG plus RPV. For each trial, DTG plus RPV was considered to be noninferior to cAR if the lower bound of the two-sided 95% confidence interval (CI) for the difference in treatment response (%) between the two regimens was greater than –10%. This NI margin was based on guidance issued by the FDA to industry for developing ARV drugs to treat HIV-1 infection.<sup>8</sup> In the most recent version of this guidance, the FDA made (non-binding) recommendations for not only conventional (non-switch) NI trials, but also for switch NI trials, in which a currently virologically suppressive ARV regimen is switched or replaced by another (usually more simplified) ARV regimen.<sup>8</sup> For conventional (non-switch) NI trials, the FDA recommends using an NI margin of –10% to –12% based on an outcome of achieving virologic suppression, while in switch NI trials, the recommended NI margin is 4% based on an outcome of minimizing loss of virologic suppression.<sup>8</sup>

The sample size for each SWORD trial was determined based on the following assumptions: an 87% treatment response in each group, an NI margin of –10%, and a 2.5% one-sided significance level. This translated into a minimum requirement of 238 patients for each group (i.e., N = 476) for each trial, and would provide 90% power to demonstrate NI between treatments on the primary efficacy outcome of the proportion of patients who maintained HIV-1 RNA below 50 copies/mL at week 48. Recruitment in each trial was planned to surpass 476 patients in order to ensure adequate numbers of patients across clinical centres for a planned substudy (DEXA) to examine the effects from treatment on bone-related outcomes in a subset of patients taking a TDF-based ARV regimen at screening.

The manufacturer notes that the protocol for each SWORD trial was approved prior to the publication of updated guidance for industry from the FDA for developing ARV drugs to treat HIV-1 infection.<sup>8</sup> This updated guidance affected both the manufacturer’s initial selection of NI margin and the primary efficacy outcome. In an attempt to align with the updated guidance, the manufacturer subsequently included a pre-planned (prior to data freeze) analysis, which compared the proportion of virologic failures (a composite outcome) between treatment groups at 48 weeks using the FDA’s stringent 4% NI margin for switch NI trials.<sup>9</sup> A pre-planned pooled analysis of the data from two SWORD trials was also performed on the primary efficacy outcome using an NI margin of –8%; however, it is not clear what the basis for this –8% NI margin was.<sup>35</sup>

The primary efficacy outcome in each SWORD trial was the proportion of patients with plasma HIV-1 RNA < 50 copies/mL at week 48 using the snapshot algorithm for the ITT-E population. The snapshot algorithm is the analytic approach preferred by the FDA.<sup>8</sup> The primary analysis set used by the manufacturer to analyze the primary efficacy outcome and assess the NI of treatments was the ITT-E. The per-protocol (PP) analysis set was used in sensitivity analyses to support the findings from the primary analysis. If both the ITT-E and PP analyses showed NI, then a pre-planned secondary analysis for superiority testing was to be conducted.<sup>35</sup>

A primary efficacy analysis stratified by baseline third-agent class and age (< or ≥ 50 years) compared the difference in treatment response between ARV regimens at week 48 using Cochran–Mantel–Haenszel (CMH) weighting to produce an adjusted estimated difference with two-sided 95% CIs. A weighted least squares chi-squared statistic was used to assess one-way homogeneity at the one-sided 10% significance level across the levels of each categorical variable individually. Exploration of any statistically significant heterogeneity was limited to the primary efficacy outcome using the week 48 snapshot analysis.

Secondary efficacy analyses repeated the snapshot analysis of the primary efficacy outcome at week 24 and again at week 48 as part of a pre-specified subgroup analysis by baseline third-agent class.

Changes in CD4+ counts were presented descriptively as the change from baseline to week 24 and to week 48. Other efficacy outcomes of interest such as HRQoL (as assessed by EQ-5D-5L) and regimen adherence (as assessed by VAS) compared the mean difference between treatment groups on the mean change in scores from baseline to week 48. Despite multiple testing of secondary outcomes, there was no statistical adjustment to control the risk of type I error.<sup>35</sup> In general, there was no imputation method used for handling missing data.<sup>9</sup>

Harms outcomes, which included the incidence of AEs and SAEs were presented descriptively for each group in each trial. Similarly, when viral resistance testing was performed based on trial-defined virologic withdrawal criteria, results were presented as the incidence of resistance-associated mutations for each group in each trial.

### *Analysis Populations*

The primary analysis set for performing efficacy analyses in both SWORD-1 and SWORD-2 was the ITT-E set, defined as all randomized patients who received at least one dose of study drug. (Table 6) It should be noted that a true ITT set consists of all randomized patients regardless of treatment received; thus, the ITT-E set in the SWORD trials would be considered a modified ITT set. The PP set was a secondary analysis set used for supporting the results of the primary efficacy analysis set (ITT-E) in the evaluation of the primary efficacy outcome. The PP included all randomized patients who received at least one dose of study drug without major protocol violation. The safety analysis set was defined in the same way as the ITT-E set.

In addition to the analysis populations, the trials also defined ITT-E subpopulations of patients who underwent viral resistance testing depending on the results of two consecutive HIV-1 RNA measurements taken at least two to four weeks apart. These included the confirmed virologic withdrawal (CVW) population, which consisted of patients with confirmed HIV-1 RNA ≥ 200 copies/mL; the potential precautionary virologic withdrawal population (pPVW), which included patients with confirmed HIV-1 RNA between 50 copies/mL and 200 copies/mL; and the precautionary virologic withdrawal (PVW) resistance population, which included all patients who met the pPVW criteria but had resistance testing performed.

**Table 6: Analysis Populations**

Analysis Set	Description
<b>SWORD-1, SWORD-2</b>	
ITT	Included all randomized patients
ITT-E	Included all randomized patients who received at least one dose of study drug
PP	Included all randomized patients who received at least one dose of study drug without major protocol violation
Safety	Included all randomized patients who received at least one dose of study drug

ITT = intention-to-treat; ITT-E = intention-to-treat exposed; PP = per-protocol.

Source: SWORD-1 Clinical Study Report;<sup>10</sup> SWORD-2 Clinical Study Report.<sup>11</sup>

### Patient Disposition

A total of 510 and 518 patients were randomized (1:1) in SWORD-1 and SWORD-2, respectively. For each trial, similar proportions of patients in the DTG plus RPV group (94%) compared with the cAR group (93%) completed the early-switch phase (Table 7). Discontinuations were primarily driven by AEs (2% versus < 1% in SWORD-1 and 4% versus < 1% in SWORD-2), protocol deviation (< 1% versus 2% for each trial), and withdrawal of consent (2% versus 3% in SWORD-1 and < 1% versus 3% in SWORD-2).

**Table 7: Patient Disposition**

Patient Disposition	SWORD-1		SWORD-2	
	DTG + RPV	cAR	DTG + RPV	cAR
<b>Screened, N</b>	669		670	
<b>Randomized, N (%)</b>	254	256	262	256
ITT population	254	256	262	256
ITT-E population	252	256	261	255
PP population	226	226	231	227
Safety population	252	256	261	255
<b>Completed<sup>a</sup> N (%)</b>	239 (94)	238 (93)	245 (94)	239 (93)
<b>Prematurely withdrawn, N (%)</b>	15 (6)	18 (7)	17 (6)	17 (7)
Adverse event	6 (2)	2 (< 1)	11 (4)	1 (< 1)
Death	0	1	1	0
Investigator discretion	0	2 (< 1)	0	1 (< 1)
Lack of efficacy	2 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)
Lost to follow-up	1 (< 1)	2 (< 1)	1 (< 1)	1 (< 1)
Protocol deviation	1 (< 1)	4 (2)	1 (< 1)	4 (2)
Patient reached protocol-defined stopping criteria	0	0	1 (< 1)	1 (< 1)
Withdrew consent	5 (2)	7 (3)	2 (< 1)	7 (3)

cAR = current antiretroviral regimen; DTG = dolutegravir; ITT = intention-to-treat; ITT-E = intention-to-treat exposed; PP = per-protocol; RPV = rilpivirine.

<sup>a</sup> Completed early-switch phase and had confirmed virologic suppression.

Source: SWORD-1 Clinical Study Report;<sup>10</sup> SWORD-2 Clinical Study Report.<sup>11</sup>

### Exposure to Study Treatments

The mean (standard deviation [SD]) exposure to treatment was similar between groups in SWORD-1 at 354.3 (47.0) days in the DTG plus RPV group compared with 354.8 (50.1) days in the cAR group. In SWORD-2, it was 350.6 (58.0) days in the DTG plus RPV group

compared with 356.3 (40.6) days in the cAR group. The proportion of patients accumulating 48 weeks to fewer than 52 weeks or  $\geq 52$  weeks of treatment exposure — which corresponded to the end of the early-switch phase and transition to the late-switch phase — was also similar between groups in SWORD-1 at 95% per group, SWORD-2 at 94% in the DTG plus RPV group, and 95% in the cAR group.

**Table 8: Exposure to Study Treatments (Safety Set)**

Exposure		SWORD-1 (n = 508)		SWORD-2 (n = 516)	
		DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)
<b>Exposure (weeks), n (%)</b>	< 2 weeks	0	1 (< 1)	3 (1)	0
	2 to < 4 weeks	0	0	1 (< 1)	1 (< 1)
	4 to < 8 weeks	2 (< 1)	2 (< 1)	0	1 (< 1)
	8 to < 12 weeks	1 (< 1)	2 (< 1)	1 (< 1)	0
	12 to < 16 weeks	1 (< 1)	0	2 (< 1)	1 (< 1)
	16 to < 20 weeks	1 (< 1)	0	1 (< 1)	0
	20 to < 24 weeks	1 (< 1)	0	0	1 (< 1)
	24 to < 28 weeks	1 (< 1)	2 (< 1)	1 (< 1)	0
	28 to < 32 weeks	1 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)
	32 to < 36 weeks	0	2 (< 1)	3 (1)	0
	36 to < 40 weeks	2 (< 1)	0	1 (< 1)	3 (1)
	40 to < 44 weeks	2 (< 1)	0	0	1 (< 1)
	44 to < 48 weeks	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
	48 to < 52 weeks	0	93 (36)	1 (< 1)	103 (40)
	$\geq 52$ weeks	239 (95)	152 (59)	244 (93)	141 (55)
<b>Exposure (days)</b>	Mean (SD)	354.3 (47.0)	354.8 (50.1)	350.6 (58.0)	356.3 (40.6)
	Median (IQR)	364.0 (364.0 to 364.0)	364.0 (362.0 to 365.0)	364.0 (364.0 to 364.0)	364.0 (361.0 to 364.0)
<b>Duration of dosing in cumulative patient years</b>		244.4	248.6	250.5	248.8

cAR = current antiretroviral regimen; DTG = dolutegravir; IQR = interquartile range; ITT = intention-to-treat; ITT-E = intention-to-treat exposed; PP = per-protocol; RPV = rilpivirine; SD = standard deviation.

Source: SWORD-1 Clinical Study Report;<sup>10</sup> SWORD-2 Clinical Study Report.<sup>11</sup>

## Critical Appraisal

### Internal Validity

- For each SWORD trial, the pre-specified NI margin was -10%. Investigators considered this NI margin, which was based on maintaining HIV-1 RNA below 50 copies/mL, reasonable for adequately preserving treatment effect. However, in 2015 — apparently after the final SWORD protocol was approved — the FDA updated its guidance for industry on developing ARV drugs in HIV-1 infection.<sup>8</sup> In this updated non-binding guidance, a distinction was made between switch and non-switch (or conventional) NI trials. For non-switch NI trials, the FDA affirmed the prior NI margin of 10% to 12%. However, for switch NI trials, the FDA recommended a stringent NI margin of 4%. The FDA established this new NI margin on the basis of virologic failure ( $\geq 50$  copies/mL) — not success (< 50 copies/mL) — and on observed virologic failure rates (1% to 3%) from

earlier switch trials whose NI margins were premised on virologic success. In response to this updated FDA guidance, the SWORD investigators conducted a pre-planned (prior to data freeze) analysis using the 4% NI margin to compare the proportion of virologic failures between groups in each trial. In addition, a pre-planned pooled analysis of the two SWORD trials using a slightly smaller 8% NI margin than was used in the primary efficacy analysis was also conducted for the primary outcome (< 50 copies/mL at week 48); it is not clear, however, what the basis for this 8% NI margin was.

- SWORD-1 and SWORD-2 were identically designed, open-label, NI trials. Randomization and stratification were performed centrally by computer software program,<sup>32</sup> thereby minimizing the risk of selection bias and promoting balance of between-treatment patient characteristics. The investigators chose an open-label instead of a double-dummy design to avoid potentially negative consequences on outcome assessment from excessive pill burdens and reduced medication adherence.<sup>32</sup> Though the open-label design may have been simpler to execute than a double-dummy design, it is possible that an assessment of comparative tolerability might have been somewhat distorted not only by the control (cAR) group's longer treatment experience (i.e., at least six months) and presumed established tolerability of their ARV regimen, but also the knowledge of treatment assignment, which could have increased AE reporting in the experimental (DTG plus RPV) group. The use of an objective primary efficacy outcome (i.e., HIV-1 RNA viral load), however, mitigates the risk of potential bias from an open-label trial design on this efficacy finding.
- Although subgroups were appropriately defined a priori and were included as stratification factors in the randomization scheme, given the NI design of the trials, subgroups add a layer of complexity to the analysis and subsequent interpretation of findings. In NI trials, each subgroup analysis generally requires a separate NI margin to assess consistency of NI, unless there is supportive evidence available to confirm that the effect of the active control does not vary meaningfully across relevant subgroups. In such a case, the NI margin from the primary analysis can be used in the subgroup analyses for comparing consistency of NI.<sup>36</sup>
- Testing for the presence of resistance-associated mutations (RAMs) was performed in patients who met virologic withdrawal criteria in whom HIV-1 RNA was confirmed  $\geq 200$  copies/mL. However, the assay used for RAM testing was not validated for use in HIV-1 RNA samples below 500 copies/mL. Thus, results from this assay may be unreliable in that not all RAMs may be detected in patients who were scheduled according to protocol to undergo RAM testing.
- Follow-up for each SWORD trial was nearly complete and non-differential between groups. For each trial, 94% in the DTG plus RPV group and 93% in the cAR group completed 48 weeks of follow-up.
- In each SWORD trial, DTG plus RPV was studied not as a co-formulated product, for which it is seeking marketing authorization, but as two separate tablets administered once daily (see Appendix 6 for assessment of bioequivalence). Despite the methodological approach taken, the CDR reviewer considered that adherence to the two separate tablets was not likely to be greater than would be expected with a co-formulated tablet; thus, this difference is not expected to overestimate the efficacy of Juluca.

- The primary analysis set used by the manufacturer to analyze the primary efficacy outcome and assess the NI of treatments was the ITT-E population. The ITT-E included all randomized patients who received at least one dose of study drug. Since a true ITT set consists of all randomized patients regardless of treatment received, the ITT-E set in the SWORD trials would be considered a modified ITT set.
- In general, there was no imputation method used for handling missing data in either SWORD trial.<sup>9</sup> In the primary efficacy analysis, for example, it appears as if patients who did not have virologic data for week 48 (4% to 5% in each group) were simply dropped from the analysis. While this lack of virologic data was non-differential between groups, the absence of these data complicates the assessment of NI.
- There were no statistical adjustments made to minimize the risk of a type I error from multiple outcome testing of secondary outcomes.<sup>35</sup> Although multiplicity of testing would not be a concern for the primary analysis, inflation of type 1 errors would be expected for the secondary, subgroup, and exploratory analyses, given the large number of statistical tests performed. As such, findings from these analyses need to be interpreted with caution.

## External Validity

- Patients recruited for the SWORD trials were mainly from Western countries — including Canada (six clinical sites in SWORD-1, seven in SWORD-2) — in North America and Europe. According to the clinical expert consulted for this review, the approach to treating HIV-1 infection is generally consistent between countries and reflective of the recommendations in the clinical practice guidelines issued by the DHHS.<sup>1</sup>
- Middle-aged, overweight, white men without hepatitis B virus coinfection made up the majority of enrolled patients in the SWORD trials. Only a fraction (approximately 7%) of patients was co-infected with HCV; these patients were not expected to require HCV treatment during their trial participation. The clinical expert consulted for this review considered these patients reflective of the type of patient encountered in contemporary clinical practice without hepatitis B or C coinfection.
- The most common ARV regimen at screening in either SWORD trial (24% in SWORD-1 and 29% in SWORD-2) was EFV/FTC/TDF. According to the clinical expert consulted for this review, this regimen is infrequently prescribed in contemporary clinical practice, having been largely displaced by abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) or elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF), which are better tolerated regimens. The early-switch phase of the SWORD trials was conducted during 2015 to 2016; the most commonly prescribed therapies at that time are no longer reflective of current clinical practice. Despite the use of these more historical regimens, however, the clinical expert indicated there was no reason to believe that appropriately virologically suppressed patients on more contemporary ARV regimens would not be eligible to switch to a dual-therapy regimen such as DTG plus RPV. However, whether DTG plus RPV would be noninferior to more contemporary ARV regimens is unclear.
- The primary efficacy outcome on which the SWORD trials' NI margin was based was the proportion of patients with HIV-1 RNA below 50 copies/mL at week 48. Since patients were beginning each trial from a point of virologic suppression (< 50 copies/mL), the more salient outcome, from a clinical — and also FDA<sup>8</sup> — point of

view would have been the loss of virologic suppression ( $\geq 50$  copies/mL) that may occur as a result of switching from a stable, virologically suppressive regimen to another regimen. In clinical practice, the consulting clinical expert for this review affirmed, any loss of virologic suppression would be undesirable.

- When initiating ARV therapy in treatment-naive patients with HIV-1 RNA above 100,000 copies/mL, RPV-based STRs (e.g., RPV/TDF/FTC or RPV/TAF/FTC) are not recommended due to the risk of virologic failure.<sup>1</sup> Because patients began the SWORD trials from a starting point of virologic suppression (HIV-1 RNA  $< 50$  copies/mL), the pre-treatment HIV-1 RNA viral load was unknown. Thus, the question arose within the CDR team whether there would be an elevated risk of virologic failure in patients assigned to DTG plus RPV if their pre-treatment HIV-1 RNA had been above 100,000 copies/mL. A review by Wood et al.<sup>5</sup> examined the SPIRIT trial, in which patients who were virologically suppressed on a boosted PI-based ARV regimen were switched to co-formulated RPV/TDF/FTC. Virologic efficacy (i.e., % of patients with HIV-1 RNA  $< 50$  copies/mL at 24 weeks) was the same between groups. The reviewer went on to cite two marketed RPV-based STRs (RPV/TDF/FTC, RPV/TAF/FTC), which have an FDA-approved indication to replace a stable, virologically suppressive regimen on condition that strict criteria are met (i.e., no history of virologic failure, HIV-1 RNA suppressed to  $< 50$  copies/mL for at least six months, no RAMs to RPV, TDF/TAF, FTC). These criteria are reflective of the entry criteria for the SWORD trials. Because of the high genetic barrier to virologic resistance offered by DTG,<sup>3,5</sup> the combination of RPV with DTG likely reduces the risk of virologic failure compared with other non-DTG, RPV-based ARV regimens. The potential concern raised by the CDR team about high pre-treatment viral load and risk of virologic failure would therefore appear to be unfounded in this therapeutic context.
- The “early-switch” phase of the SWORD trials, upon which this submission is based, ran 48 weeks, which is consistent with the minimum required follow-up time set by the FDA for ARV drug development using an NI switch-trial design.<sup>8</sup>

## Efficacy

Only those efficacy outcomes identified in the review protocol (see Table 3 ) are reported. “Key efficacy outcomes” are presented in tabular format (Table 9) while “other efficacy outcomes” may be viewed in tabular format in Table 14 in Appendix 4.

### Proportion of Patients With HIV-1 RNA $\geq 50$ Copies/mL at 48 Weeks

The proportion of patients with HIV-1 RNA  $\geq 50$ copies/mL at 48 weeks was identified as the most important efficacy outcome by the CDR review team (and also by the FDA8); it was examined in the SWORD trials as a pre-planned (prior to data freeze) analysis, specifically, as the proportion of patients who were classified as snapshot virological failure at week 48.



The most common reason for being classified as a virologic failure was discontinuation due to lack of efficacy (Table 9). In SWORD-1, a similar proportion of patients taking DTG plus RPV (< 1%) compared with cAR (< 1%) were classified as virologic failures at week 48 (difference: 0.0%; 95% CI, -1.3% to 1.4%). Likewise, in SWORD-2, less than 1% of patients taking DTG plus RPV compared with 2% taking cAR were classified as virologic failures at week 48 (difference: -1.0%; 95% CI, -2.4% to 0.5%). In the pooled analysis, less than 1% of patients taking DTG plus RPV compared with 1% of patients taking cAR were classified as virologic failures at week 48 (difference: -0.5%; 95% CI, -1.4% to 0.5%). In all analyses, the upper bound of the 95% CI was less than the 4% NI margin recommended by the FDA.

### Proportion of Patients With HIV-1 RNA < 50 copies/mL at 48 Weeks

In the primary (ITT-E) analysis for SWORD-1, a similar proportion of patients taking DTG plus RPV (95%) compared with cAR (96%) maintained HIV-1 RNA below 50 copies/mL at week 48 (difference: -0.6%; 95% CI, -4.3% to 3.0%). The secondary (PP) analysis supported the primary analysis.

In the primary (ITT-E) analysis for SWORD-2, a similar proportion of patients taking DTG plus RPV (94%) compared with cAR (94%) maintained HIV-1 RNA below 50 copies/mL at week 48 (difference: 0.2%; 95% CI, -3.9% to 4.2%). The secondary (PP) analysis supported the primary analysis.

In the primary (ITT-E) analysis for the pooled trials, a similar proportion of patients taking DTG plus RPV (95%) compared with cAR (95%) maintained HIV-1 RNA below 50 copies/mL at week 48 (difference: -0.2%; 95% CI, -3.0% to 2.5%). The secondary (PP) analysis supported the primary analysis.

In all three of the previously described analyses, the NI margin of -10% that was pre-specified by the manufacturer was met.



**Table 9: Key Efficacy Outcomes**

Virologic Efficacy Outcomes	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
<b>Virologic failure<sup>a</sup></b>						
N (%), ITT-E	2 (< 1)	2 (< 1)	1 (< 1)	4 (2)	3 (< 1)	6 (1)
Adjusted difference in proportion, % (CI) <sup>b</sup>	0.0 (-1.3, 1.4)		-1.0 (-2.4, 0.5)		-0.5 (-1.4, 0.5)	
<b>Virologic failures included any of the following:</b>						
• Data in window not < 50 copies/mL	0	1 (< 1)	0	1 (< 1)	0	2 (< 1)
• Discontinued for lack of efficacy	2 (< 1)	0	0	2 (< 1)	2 (< 1)	2 (< 1)
• Discontinued for other reason while not < 50 copies/mL	0	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)
• Change in ART	0	0	0	1 (< 1)	0	1 (< 1)
<b>Virologic success</b>						
HIV-1 RNA < 50 copies/mL at week 48, N (%), ITT-E	240 (95)	245 (96)	246 (94)	240 (94)	486 (95)	485 (95)
Adjusted difference in proportion, % (CI) <sup>c</sup>	-0.6 (-4.3, 3.0)		0.2 (-3.9, 4.2)		-0.2 (-3.0, 2.5)	
HIV-1 RNA < 50 copies/mL at week 48, N (%), PP	217 (96)	218 (96)	220 (95)	217 (96)	437 (96)	435 (96)
Adjusted difference in proportion, % (CI) <sup>c</sup>	-0.6 (-4.1, 2.9)		-0.4 (-4.3, 3.5)		-0.5 (-3.1, 2.1)	

ART = antiretroviral therapy; cAR = current antiretroviral regimen; CI = 95% confidence interval; DTG = dolutegravir; INSTI = integrase strand transfer inhibitor; ITT-E = intention-to-treat exposed; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PP = per-protocol; RNA = ribonucleic acid; RPV = rilpivirine.

<sup>a</sup> Pre-planned analysis.

<sup>b</sup> Based on Cochran–Mantel–Haenszel (CMH) stratified analysis adjusting for age (< 50, ≥ 50 years old) and baseline third-agent class (PI, NNRTI, INSTI).

<sup>c</sup> Difference: Proportion on (DTG + RPV) — Proportion on cAR; based on CMH stratified analysis adjusting for age (< versus ≥ 50 years old) and baseline third agent (PI, NNRTI, INSTI)

Source: SWORD-1 Clinical Study Report;<sup>10</sup> SWORD-2 Clinical Study Report.<sup>11</sup>

### Subgroup Analyses

The following subgroups were identified as being of interest to the CDR review team for assessing any differences in treatment effect: baseline viral load prior to suppressive triple-ARV regimen; baseline CD4+ count prior to suppressive triple-ARV regimen; biological sex; and baseline ARV regimen third-agent class (i.e., NNRTI, boosted PI, INSTI). Subgroup analyses were only conducted on the key efficacy outcome describing the proportion of patients with HIV-1 RNA below 50 copies/mL at 48 weeks. Of the four subgroups of interest, only data for biological sex and baseline ARV regimen third-agent class were available. Data are presented in tabular form in Table 13 in Appendix 4. It should be noted that the subgroups were not evaluated against any NI margin specific to the subgroups, as is generally appropriate for NI trials. Thus, it is not possible to evaluate NI in this context.

## Biological Sex

### *Female Patients*

In SWORD-1, similar proportions of female patients taking DTG plus RPV (91%) compared with cAR (90%) maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: 1.2%; 95% CI, -9.7% to 12.1%). In SWORD-2, similar proportions of female patients taking DTG plus RPV (94%) compared with cAR (91%) likewise maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: 2.3%; 95% CI, -7.2% to 11.9%).

### *Male Patients*

In SWORD-1, similar proportions of male patients taking DTG plus RPV (96%) compared with cAR (97%) maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: -0.7%; 95% CI, -4.2% to 2.8%). In SWORD-2, similar proportions of male patients taking DTG plus RPV (94%) compared with cAR (95%) likewise maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: -0.5%; 95% CI, -4.9% to 3.9%).

## Baseline ARV Regimen Third-Agent Class

### *Protease Inhibitor*

In SWORD-1, among patients who had been taking a PI as the third-agent class in their baseline ARV regimen, 95% of patients assigned DTG plus RPV, compared with 92% of patients assigned to cAR-maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: 2.8% (95% CI, -5.3% to 10.8%). Likewise, in SWORD-2, 91% of patients assigned to DTG plus RPV compared with 97% of patients assigned to cAR-maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: -5.4% (95% CI, -13.9% to 3.1%).

### *Non-Nucleoside Reverse Transcriptase Inhibitor*

In SWORD-1, among patients who had been taking a NNRTI as the third-agent class in their baseline ARV regimen, 95% of patients assigned to DTG plus RPV compared with 98% of patients assigned to cAR-maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: -3.1%; 95% CI, -7.7% to 1.5%). Likewise, in SWORD-2, 97% of patients assigned to DTG plus RPV compared with 93% of patients assigned to cAR-maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: 3.5%; 95% CI, -1.6% to 8.6%).

### *Integrase Strand Transfer Inhibitor*

In SWORD-1, among patients who had been taking an INSTI as the third-agent class in their baseline ARV regimen, 98% of patients assigned DTG plus RPV compared with 96% of patients assigned to cAR-maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: 2.0%; 95% CI, -5.1% to 9.0%). Likewise, in SWORD-2, 92% of patients assigned to DTG plus RPV compared with 94% of patients assigned to cAR-maintained HIV-1 RNA below 50 copies/mL from baseline to 48 weeks (difference: -2.4%; 95% CI, -12.1% to 7.4%).

## Other Efficacy Outcomes

## CD4+ Count

In both SWORD-1 and SWORD-2, the median CD4+ count increased from baseline to week 48. In SWORD-1, the median (interquartile range [IQR]) increase was 25.0 (–68 to 119) cells/mm<sup>3</sup> in the DTG plus RPV group and 35.0 (–37.0 to 104.0) cells/mm<sup>3</sup> in the cAR group. In SWORD-2, the median (IQR) increase was 29.0 (–47.0 to 108) cells/mm<sup>3</sup> in the DTG plus RPV group and 13.0 (–59.0 to 108.0) cells/mm<sup>3</sup> in the cAR group.

## Development of Drug Resistance

Patients who met viral resistance–testing criteria with confirmed HIV-1 RNA  $\geq$  200 copies/mL included the CVW population. The development of drug resistance was uncommon in either SWORD trial. In SWORD-1, there was one patient from each group who was classified as CVW. A RAM affecting the INSTI class was only documented in the patient from the DTG plus RPV group; however, this particular mutation was present at baseline and did not affect susceptibility to DTG. Similar results were found in SWORD-2, where one patient from each group was classified as CVW, with only the patient in the DTG plus RPV group documenting an NNRTI RAM, which did not affect susceptibility to RPV. No RAMS were detected in the samples from the two cAR groups. All four patients were withdrawn from study treatment.

## Health-Related Quality of Life

HRQoL, as assessed by the EQ-5D-5L, was virtually unchanged from baseline to week 48. In SWORD-1, the mean difference in utility score between DTG plus RPV and cAR was 0.004 (95% CI, –0.011 to 0.018;  $P = 0.603$ ). In SWORD-2, that difference was –0.002 (95% CI, –0.0017 to 0.013;  $P = 0.821$ ).

## Adherence to Antiretroviral Regimen

In addition to standard pill counts at each study visit, adherence to the assigned antiretroviral regimen was assessed using a VAS, by which patients self-rated their level of adherence on a scale ranging from 0 to 100. In both trials the change in self-rated adherence from baseline to week 48 was negligible. In SWORD-1, the mean (SD) change from baseline to week 48 was –0.47 (3.9) in the DTG plus RPV group compared with –0.25 (3.6) in the cAR group. In SWORD-2, the mean (SD) change was –0.54 (4.5) in the DTG plus RPV group compared with 0.05 (4.2) in the cAR group.

## Harms

Only those harms identified in the review protocol (Table 3) are reported subsequently. See Table 10 for a summary of harms data and Appendix 4 for more detailed tabular presentations of harms data.

## Adverse Events

The overall frequency of AEs was slightly higher in the DTG plus RPV group compared with the cAR group for both SWORD-1 (79% versus 74%) and SWORD-2 (75% versus 68%). However, the frequency of individual AEs was similar between groups in each trial. The most commonly reported AEs included nasopharyngitis (10%), headache (6%), upper respiratory tract infection (6%), diarrhea (6%), back pain (4%), bronchitis (4%), influenza (3%), and arthralgia (3%).

## Serious Adverse Events

The overall frequency of SAEs was similar between the DTG plus RPV and cAR groups in SWORD-1 (4% versus 5%) and SWORD-2 (7% versus 4%). The most common SAEs by system organ class were infections and infestations (< 1% versus 2% in SWORD-1; 3% versus 0% in SWORD-2) and injury, poisoning, and procedural complications (< 1% versus 0% in SWORD-1; 1% versus 1% in SWORD-2).

## Withdrawals Due to Adverse Events

The overall frequency of withdrawals due to adverse events (WDAEs) was slightly higher in the DTG plus RPV group compared with the cAR group in SWORD-1 (4% versus < 1%) and SWORD-2 (5% versus < 1%). The most common WDAEs by system organ class were psychiatric disorders (2% versus 0% in SWORD-1; 2% versus < 1% in SWORD-2) and gastrointestinal disorders (1% versus 0% in SWORD-1; 2% versus 0% in SWORD-2).

## Mortality

A total of two deaths were recorded during the early-switch phase of the SWORD trials, one in SWORD-1 and one in SWORD-2. In SWORD-1, one death due to malignant neoplasm of the lung was reported in the cAR group. In SWORD-2, one death due to Kaposi sarcoma was reported in the DTG plus RPV group.

## Notable Harms

Notable harms were identified through input submitted by patient groups (See Patient Input Summary in Appendix 1) and through discussion with the clinical expert consulted for this review. These notable harms were broadly categorized as bone-related and renal-related harms. Bone-related harms, which would ideally include data on the incidence of fractures and changes in bone mineral density (BMD), were specifically addressed in the DEXA substudy<sup>37</sup> submitted as a separate Clinical Study Report by the manufacturer. A high-level summary of the outcomes of interest from the DEXA substudy is presented here, while a more detailed review is provided as a Supplemental Issue in Appendix 7. Renal-related harms were evaluated from changes in serum creatinine, estimated glomerular filtration rate (eGFR), urine albumin to creatinine ratio, urine protein to creatinine ratio, and urine glucose. These renal-related harms were reported in the SWORD trials and thus are included in Table 10.

### *Bone-Related*

The aim of the pre-specified DEXA substudy (n = 102) was to compare the safety of DTG plus RPV versus cAR on bone-related outcomes in a subset of patients from the SWORD trials who were taking a TDF-based ARV regimen at screening. The primary safety end point in the DEXA substudy was the percentage change from baseline at week 48 in total hip BMD as assessed by areal density ( $g/cm^2$ ). The percentage change from baseline at week 48 in lumbar spine BMD, as assessed by areal density ( $g/cm^2$ ), was a secondary outcome. The clinical expert consulted on this review confirmed that assessments of the hip and spine would be the key anatomical sites for evaluating adverse consequences on BMD from treatment. Fracture incidence was not an outcome in the DEXA substudy. Of the 102 patients included in the DEXA substudy, 81 (79%) were evaluable (i.e., had dual-energy X-ray absorptiometry [DXA] scans performed at baseline and week 48). Of these, 46 were taking DTG plus RPV and 35 were taking a TDF-based cAR. At baseline, mean (SD) areal

density was similar between groups for total hip (0.964 [0.15] g/cm<sup>2</sup> versus 0.974 [0.11] g/cm<sup>2</sup>) and lumbar spine (1.063 [0.16] g/cm<sup>2</sup> versus 1.086 [0.15] g/cm<sup>2</sup>) sites. From baseline to week 48, total hip areal density increased in both groups (1.34% in the DTG plus RPV group versus 0.05% in the TDF-based cAR group). This translated into an adjusted between-group mean difference of 1.29% (95% CI, 0.27% to 0.31%; *P* = 0.014). For the lumbar spine, areal density likewise increased in both groups (1.46% in the DTG plus RPV group versus 0.15% in the TDF-based cAR group) from baseline to week 48. This translated into an adjusted between-group mean difference of 1.32% (95% CI, 0.07% to 2.57%; *P* = 0.039).

### *Renal-Related*

Mean (SD) serum creatinine was similar at baseline between DTG plus RPV and cAR groups in SWORD-1 (78.4 [15.5] µmol/L versus 78.2 [13.9] µmol/L) and SWORD-2 (76.4 [14.5] µmol/L versus 77.8 [15.4] µmol/L), then rose slightly in the DTG plus RPV group (7.6 [9.5] µmol/L in SWORD-1; 8.8 [9.3] µmol/L in SWORD-2) compared with the cAR group (0.9 [7.8] µmol/L in SWORD-1; -0.3 [7.5] µmol/L in SWORD-2) from baseline to 48 weeks. At baseline, eGFR was similar between DTG plus RPV and cAR groups: 100.0 (18.2) mL/min/1.73 m<sup>2</sup> versus 100.7 (16.3) mL/min/1.73 m<sup>2</sup> in SWORD-1; 101.4 (16.4) mL/min/1.73 m<sup>2</sup> versus 100.1 (15.5) mL/min/1.73 m<sup>2</sup> in SWORD-2.

The eGFR, which is influenced by changes in serum creatinine, decreased slightly from baseline to 48 weeks in the DTG plus RPV group (-8.3 [10.3] mL/min/1.73 m<sup>2</sup> in SWORD-1; -10.0 [9.9] mL/min/1.73 m<sup>2</sup> in SWORD-2) compared with the cAR group (-1.4 [7.9] mL/min/1.73 m<sup>2</sup> in SWORD-1; -0.2 [7.9] mL/min/1.73 m<sup>2</sup> in SWORD-2). Median (range) urine albumin to creatinine ratio (ACR) was comparable between the DTG plus RPV and cAR groups at baseline in SWORD-1 (0.60 [0.2 to 69.3] versus 0.70 [0.2 to 484.8]) and SWORD-2 (0.60 [0.1 to 83.3] versus 0.60 [0.2 to 127.2]). ACR was essentially unchanged in both groups from baseline to week 48. Similarly, median (range) urine protein to creatinine ratio (PCR) was comparable between the DTG plus RPV and cAR groups at baseline in SWORD-1 (8.70 [2.0 to 185.8] versus 9.20 [2.6 to 701.5]) and SWORD-2 (8.60 [3.4 to 180.2] versus 8.10 [3.1 to 148.5]). PCR was also essentially unchanged in both groups from baseline to week 48. Baseline dipstick urine glucose results were not reported for either SWORD trial. At 48 weeks, urine dipstick results were “negative” for approximately 99% of patients overall, regardless of treatment assignment or trial.

**Table 10: Harms**

Adverse Events	SWORD-1		SWORD-2		Pooled		
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)	
Patients with > 0 AEs, N (%)	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)	
Most common AEs <sup>a</sup>							
Nasopharyngitis	28 (11)	28 (11)	21 (8)	22 (9)	49 (10)	50 (10)	
Headache	23 (9)	17 (7)	18 (7)	6 (2)	41 (8)	23 (5)	
Upper respiratory tract infection	7 (3)	10 (4)	17 (7)	27 (11)	24 (5)	37 (7)	
Diarrhea	21 (8)	16 (6)	11 (4)	11 (4)	32 (6)	27 (5)	
Back pain	9 (4)	19 (7)	6 (2)	12 (5)	15 (3)	31 (6)	
Bronchitis	7 (3)	5 (2)	16 (6)	10 (4)	23 (4)	15 (3)	
Influenza	4 (2)	13 (5)	10 (4)	4 (2)	14 (3)	17 (3)	
Arthralgia	8 (3)	4 (2)	13 (5)	5 (2)	21 (4)	9 (2)	
<b>SAEs</b>							
Patients with > 0 SAEs, N (%)	9 (4)	12 (5)	18 (7)	9 (4)	27 (5)	21 (4)	
Most common SAEs <sup>a</sup>							
Infections and infestations, any event	2 (< 1)	6 (2)	8 (3)	0	10 (2)	6 (1)	
Injury, poisoning, and procedural complications, any event	1 (< 1)	0	3 (1)	3 (1)	4 (< 1)	3 (< 1)	
<b>WDAEs</b>							
WDAEs, N (%)	9 (4)	2 (< 1)	12 (5)	1 (< 1)	21 (4)	3 (< 1)	
Most common reasons							
Psychiatric disorders, any event	4 (2)	0	5 (2)	1 (< 1)	9 (2)	1 (< 1)	
Gastrointestinal disorders, any event	3 (1)	0	4 (2)	0	7 (1)	0	
<b>Deaths</b>							
Number of deaths, N (%)	0	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)	
Most common reasons							
Kaposi sarcoma	0	0	1 (< 1)	0	1 (< 1)	0	
Lung neoplasm malignant	0	1 (< 1)	0	0	0	1 (< 1)	
<b>Notable Harms</b>							
<i>Renal-related:</i>							
Serum creatinine (µmol/L)							
N (%)	238 (94)	243 (95)	245 (94)	241 (95)	483 (94)	484 (95)	
Baseline, mean (SD)	78.4 (15.5)	78.2 (13.9)	76.4 (14.5)	77.8 (15.4)	77.4 (15.0)	78.0 (14.7)	
Change from baseline to week 48, mean (SD)	7.6 (9.5)	0.9 (7.8)	8.8 (9.3)	-0.3 (7.5)	8.2 (9.4)	0.3 (7.7)	
eGFR (mL/min/1.73 m <sup>2</sup> ) <sup>c</sup>							
N (%)	238 (94)	243 (95)	245 (94)	241 (95)	483 (94)	484 (95)	
Baseline, mean (SD)	100.0 (18.2)	100.7 (16.3)	101.4 (16.4)	100.1 (15.5)	100.7 (17.3)	100.4 (15.9)	
Change from baseline to week 48, mean (SD)	-8.3 (10.3)	-1.4 (7.9)	-10.0 (9.9)	-0.2 (7.9)	-9.2 (10.1)	-0.8 (7.9)	
Urine albumin to creatinine ratio ( mg/mmol)							
N (%)	Baseline	218 (87)	223 (87)	227 (87)	226 (89)	445 (87)	449 (88)
	Week 48	166 (66)	171 (67)	178 (68)	181 (71)	344 (67)	352 (69)
Baseline, median (range)	0.60 (0.2 to 69.3)	0.70 (0.2, 484.8)	0.60 (0.1, 83.3)	0.60 (0.2, 127.2)	0.60 (0.1, 83.3)	0.60 (0.2, 484.8)	

		SWORD-1		SWORD-2		Pooled	
Change from baseline to week 48, median (range)		-0.10 (-22.7 to 2.6)	-0.10 (-366.7 to 12.6)	-0.15 (-57.1 to 13.3)	0.00 (-126.7 to 13.0)	-0.10 (-57.1 to 13.3)	-0.05 (-366.7 to 13.0)
Urine protein to creatinine ratio ( mg/mmol)							
N (%)	Baseline	223 (88)	219 (86)	230 (88)	224 (88)	453 (88)	443 (87)
	Week 48	176 (70)	182 (71)	192 (74)	193 (76)	368 (72)	375 (73)
Baseline, median (range)		8.70 (2.0 to 185.8)	9.20 (2.6 to 701.5)	8.60 (3.4 to 180.2)	8.10 (3.1 to 148.5)	8.60 (2.0 to 185.8)	8.60 (2.6 to 701.5)
Change from baseline to week 48, median (range)		-1.90 (-175.6 to 7.7)	0.45 (-554.6 to 117.2)	-1.40 (-152.9 to 23.4)	0.30 (-15.1 to 28.1)	-1.60 (-175.6 to 23.4)	0.40 (-554.6 to 117.2)
Urine glucose (dipstick)							
Negative at baseline, n (%)		NR	NR	NR	NR	NR	NR
Negative at week 48, n (%)		225 (> 99)	229 (99)	235 (98)	235 (> 99)	460 (99)	464 (> 99)
<i>Bone-related</i>		Refer to supplemental issue: "DEXA substudy"					

AE = adverse event; cAR = current antiretroviral regimen; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; NR = not reported; RPV = rilpivirine; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

<sup>a</sup> Frequency ≥ 5%.

<sup>b</sup> Frequency > 1%.

<sup>c</sup> Employing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Source: SWORD-1 Clinical Study Report;<sup>10</sup> SWORD-2 Clinical Study Report.<sup>11</sup>



## Discussion

### Summary of Available Evidence

The evidence for this review was drawn from two identical phase III (SWORD-1, n = 510; SWORD-2, n = 518) randomized (1:1), multi-centre, open-label, active-controlled, parallel-group, NI trials. The first 48 weeks, known as the “early-switch” phase, was the basis for seeking market authorization. Patients who were virologically suppressed (HIV-1 RNA < 50 copies/mL) at baseline were randomly assigned to switch to an experimental dual-ARV regimen of DTG 50 mg plus RPV 25 mg taken once daily, or to continue their current triple-ARV therapy regimen (cAR) for 48 weeks. The primary efficacy outcome in both trials was the proportion of patients with plasma HIV-1 RNA below 50 copies/mL at week 48 using the snapshot algorithm for the ITT-E population. The pre-specified NI margin for the primary outcome in each trial was –10%. The NI margin was selected prior to the FDA updating its (non-binding) guidance for industry on developing ARV drugs to treat HIV-1 infection, in which a stringent NI margin of 4% based on an outcome of virologic suppression was added for switch NI trials.<sup>8</sup> The remaining 52 to 148 weeks (late-switch phase) of the SWORD studies were non-comparative in design and constituted a long-term extension intended to support the findings from the early-switch phase and provide some evidence of treatment durability.

### Interpretation of Results

#### Efficacy

A major drawback of the SWORD trials was the selection of the NI margin, which was based on a trial designed to show NI between treatments on the outcome of maintaining virologic suppression. Neither the margin nor the outcome upon which the margin was based is consistent with current FDA guidance.<sup>8</sup> Updated industry guidance issued by the FDA<sup>8</sup> (after the SWORD protocol was apparently finalized) established a new stringent NI margin of 4% specifically intended for NI switch trials. Because patients in NI switch trials begin from a point of virologic suppression (< 50 copies/mL), the more salient outcome, in the FDA’s point of view, is the loss of virologic suppression ( $\geq 50$  copies/mL) that could occur as a result of switching from a stable, virologically suppressive regimen to another regimen. The SWORD trials, whose patients were virologically suppressed below 50 copies/mL at baseline, used a traditional NI margin of –10%, which was premised on achieving maximal virologic suppression (not on minimizing loss of virologic control). This approach would have been consistent with previously issued, undifferentiated FDA guidance for NI trials, had SWORD patients not already been virologically suppressed to below 50 copies/mL at baseline. Although the investigators sought to address the new FDA guidance by conducting a week 48 pre-planned (prior to data freeze) analysis of the proportion of “virologic failures,” the fact remains that the original SWORD trials were not designed to evaluate NI based on a primary efficacy outcome of loss of virologic suppression ( $\geq 50$  copies/mL) in accordance with contemporary FDA guidance for NI switch trials.<sup>8</sup>

In both SWORD-1 and SWORD-2, the proportion of patients with virologic failure at week 48 was low between groups. A pre-planned analysis of the pooled data showed a similar proportion of patients taking DTG plus RPV (< 1%) compared with cAR (1%) who were classified as virologic failures at week 48 (difference: –0.5%; 95% CI, –1.4% to 0.5%).



Although the upper bound of the 95% CI was less than the 4% NI margin recommended by the FDA, the analysis was not controlled for multiplicity, complicating the interpretation of these findings.

In the primary (ITT-E) efficacy analysis of the proportion of patients with HIV-1 RNA below 50 copies/mL at 48 weeks, both SWORD trials produced similar results between the DTG plus RPV and cAR groups (SWORD-1: 95% versus 96%; SWORD-2: 94% versus 94%) with a pooled difference of -0.2% (95% CI, -3.0% to 2.5%). The secondary PP analysis supported the findings from the primary analysis. In each trial, the manufacturer's pre-specified NI margin of -10%, which was reduced to -8% for the pooled analysis, was met, since the lower bound of the 95% CI did not cross -10% in the case of the individual trials, or -8% in the case of the pooled analysis.

The following subgroups were identified as being of interest to the CDR review team for assessing any differences in treatment effect: baseline viral load prior to suppressive triple-ARV regimen; baseline CD4+ count prior to suppressive triple-ARV regimen; biological sex; and baseline ARV regimen third-agent class (i.e., NNRTI, boosted PI, INSTI). Subgroup analyses were only conducted on the key efficacy outcome describing the proportion of patients with HIV-1 RNA below 50 copies/mL at 48 weeks. Of the four subgroups of interest, only data for biological sex and baseline ARV regimen third-agent class were available. Assessment of NI across subgroups was hindered by both the absence of NI margins for each subgroup and the lack of statistical power considerations for subgroup analyses.

Other, non-virologic efficacy outcomes examined in the SWORD trials included changes in CD4+ counts, development of RAMs, and changes in self-reported ARV regimen adherence, which were presented descriptively; changes in HRQoL were analyzed for differences between groups.

In both SWORD-1 and SWORD-2, the median CD4+ count increased modestly and similarly in each group from baseline to week 48 (pooled: DTG plus RPV: 28.0 cells/mm<sup>3</sup>; cAR: 22.0 cells/mm<sup>3</sup>). According to the clinical expert consulted for this review, the magnitude of the increase was appropriately small, given that patients were virologically suppressed to fewer than 50 copies/mL at baseline.

The development of RAMs was uncommon in either SWORD trial. Patients who met viral resistance testing criteria with confirmed HIV-1 RNA  $\geq$  200 copies/mL were referred for virologic resistance testing. In SWORD-1, one patient from the DTG plus RPV group had a RAM affecting the INSTI class, but this particular mutation had been present at baseline and did not impact susceptibility to DTG. In SWORD-2, one patient from the DTG plus RPV group had a RAM affecting the NNRTI class, which did not impact susceptibility to RPV. No RAMS were detected in the samples from the cAR groups.

Self-reported ARV regimen adherence, as assessed by VAS (range: 0 to 100) was about 98 at baseline for both groups in each trial. Within-group mean changes from baseline to week 48 were negligible and ranged from 0.05 to -0.54. Tablet size has been identified by the clinical expert consulted on this review and others<sup>38</sup> as a potential factor influencing adherence to ARV therapy. According to the clinical expert, most currently marketed STRs are considered large-tablet regimens, which can make swallowing difficult for some patients. Measuring 9.1 mm and 6.4 mm, respectively, DTG plus RPV is considered a small-tablet regimen, particularly when compared with co-formulated NRTI drug combinations (e.g., TDF/FTC, ABC/3TC), which measure more than 17 mm in size.<sup>38</sup> The

tablet size of the marketed co-formulation of DTG plus RPV is not reported, however, since the tablets were studied as separate entities in the SWORD trials. It is possible that a DTG/RPV STR may promote better long-term adherence in patients who have trouble swallowing large tablets. Despite its potential size advantage, because of the RPV component, DTG plus RPV requires co-administration with food and avoidance of concurrent antacids,<sup>3,19</sup> which may be inconvenient for some patients.

The mean change in HRQoL, as assessed by the EQ-5D-5L, was similarly negligible between groups from baseline to week 48 for each SWORD trial (pooled difference: 0.001 [95% CI, -0.009 to 0.011;  $P = 0.847$ ]). This finding is not surprising, given that patients began the trials already maximally virologically suppressed and with high baseline HRQoL scores.

At the request of the CDR review team, the manufacturer provided a limited data set for the ongoing late-switch phase (weeks 52 to 148), covering up to week 100.<sup>39</sup> These late-switch phase data are summarized in Appendix 6. The purpose of the late-switch phase was to support the findings of the early-switch phase and to provide some evidence of durability of treatment. Those patients who were initially randomized to continue their cAR during weeks 0 to 48, with confirmed virologic suppression at week 48, were switched to DTG plus RPV during weeks 48 to 52; thus, all patients were taking DTG plus RPV from weeks 52 to 148.

[REDACTED]

At the time of this pre-Notice of Compliance CDR review, there were no published regulatory or health technology assessment reports available for comparison of findings. However, the *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living With HIV* issued by the DHHS,<sup>1</sup> which the clinical expert consulted for this review confirmed are the key clinical practice guidelines in use by practitioners, do address the emerging evidence for dual-therapy ARV regimens. The DHHS guidelines assert that maintaining virologic suppression without compromising future treatment options is of the utmost importance when considering a switch from a virologically suppressive triple-ARV regimen to a dual-therapy regimen. For switching to a two-drug regimen in the setting of a stable, virologically suppressive triple-ARV regimen, the DHHS guidelines mention two regimen options that it considers to have good supporting evidence: a boosted PI plus FTC or 3TC, or DTG plus RPV.<sup>1</sup> In the case of the DTG plus RPV regimen, the evidence cited comes from the SWORD trials.<sup>1</sup> Specifically, the DHHS states “DTG plus RPV can be a reasonable option when the use of NRTIs is not desirable and when resistance to either DTG or RPV is not expected.”<sup>1</sup> This statement is given a “strong” rating.<sup>1</sup>

## Harms

The overall frequency of AEs was slightly higher in the DTG plus RPV group compared with the cAR group for both SWORD-1 (79% versus 74%) and SWORD-2 (75% versus 68%). This was not unexpected, given that the cAR group began the trial having had at least six months prior exposure to their ARV treatment regimen, unlike the (experimental) DTG plus RPV group. Nonetheless, the frequency of individual AEs was similar between groups in each trial. The overall frequency of SAEs was similar between the DTG plus RPV and cAR groups (pooled: 5% versus 4%) while WDAEs were slightly higher in the DTG plus RPV group (pooled: 4% versus < 1%). Two deaths were recorded: one in SWORD-1 (cAR group: malignant neoplasm of the lung) and one in SWORD-2 (DTG plus RPV group: Kaposi sarcoma). Notable harms identified by patient groups and through discussion with the clinical expert consulted for this review included bone-related (i.e., fracture incidence, changes in BMD) and renal-related (i.e., various indicators of renal function and structure) harms (Table 1). Bone-related harms (changes in BMD but not fracture incidence) were specifically addressed in the DEXA substudy (Appendix 7) and showed small increases in areal density of the hip and lumbar spine, with DTG plus RPV treatment compared with TDF-based cAR. The clinical expert consulted for this review considered these BMD increases directionally reassuring, but unlikely to be clinically meaningful. There was no indication of an adverse impact on renal function or structure from short-term (i.e., 48 weeks) exposure to DTG plus RPV treatment.

As described earlier, the manufacturer provided a limited data set for the ongoing late-switch phase (weeks 52 to 148), covering up to week 100 at the CDR team's request.<sup>39</sup> These late-switch phase data are summarized in Appendix 6. [REDACTED]

DTG appears to be a well-tolerated drug with few drug–drug interactions.<sup>3</sup> It also has the advantage of a high genetic barrier to resistance.<sup>3</sup> RPV must be taken with food and cannot be taken with acid-suppressing drugs.<sup>3</sup> It is also associated with a number of clinically important drug–drug interactions because it is a substrate for CYP 3A4.<sup>3</sup> DTG plus RPV were administered separately as individual drugs during the SWORD trials, but the regimen is seeking market authorization as a co-formulated or single-tablet regimen. To that end, supporting bioequivalence studies were submitted and confirm bioequivalence between the individual components and the co-formulated product (Appendix 5).

## Potential Place in Therapy<sup>1</sup>

For the treatment of HIV-infected individuals without previous virologic failure, which constitutes the majority of HIV-infected individuals in Canada, there are many options available, including six STRs (Atripla, Complera, Odefsey, Stribild, Genvoya and Triumeq). These STRs, and almost all widely used treatments otherwise, consist of NRTIs and a third component (PI, NNRTI or INSTI), with or without a pharmacokinetic booster. Juluca, as an STR and as an antiviral regimen in general, differs in having only two components, neither of which is an NRTI.

<sup>1</sup> This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Although treatment alternatives are welcome, there are no significant unmet needs for patients with a non-resistant virus in this era of HIV antiviral therapy. The available antivirals offer STR options for the majority of individuals infected with non-resistant HIV. These antivirals are convenient and increasingly free of immediate and long-term toxicities; drug interactions can occur but are manageable in most cases.

It is rare that a patient cannot tolerate the NRTI components of the available STRs. However, the safe use of NRTIs may be limited in patients with advanced renal failure (TAF use is not recommended with creatinine clearance below 30 mL/min, and 3TC dosing must be adjusted for reduced creatinine clearance) or in the rarer event of patients presenting with emerging lipoatrophy on NRTI-containing regimens. The specific use of ABC is not recommended in patients with HLA B5701 positivity because of the risk of a hypersensitivity reaction. These patients and others who report symptoms possibly attributable to the NRTIs, like sexual dysfunction or fatigue, might benefit from Juluca.

Probably those most likely to switch to Juluca, and most likely to benefit from it, would be patients who experience financial hardship because of the cost of their current STR. The monthly cost of the other STRs exceeds that of Juluca by \$400 or more. As well, Juluca is a smaller tablet than Genvoya or Triumeq, making it an attractive option for some. The requirement for Juluca to be taken with food and without antacids, however, might limit its use somewhat.

Assuming personal costs are not excessive, most patients are satisfied with the currently available regimens. There is little discussion raised by patients for the need for nucleoside-sparing regimens or those with fewer antiviral components. As such, it is anticipated that clinicians will initiate the conversation about switching. Overall, the smaller size and lower price of Juluca would likely prompt many patients stabilized on another treatment regimen to consider switching to Juluca. These would be more important considerations for switching than the need for a regimen that is free of NRTIs or has fewer drug components; it is expected that perhaps 60% of treated individuals in Canada might be candidates for Juluca.

## Conclusions

In two phase III NI randomized controlled trials, patients who were switched from a stable, virologically suppressive (HIV-1 RNA < 50 copies/mL) triple-ARV regimen to a dual-therapy ARV regimen of DTG plus RPV maintained similar rates of viral load suppression (approximately 95%) after 48 weeks of treatment as the patients who remained on their stable, virologically suppressive triple-therapy ARV regimen. Virologic failure rates were low ( $\leq 2\%$ ) in both groups in both trials after 48 weeks of treatment. Other efficacy outcomes were generally supportive of the primary efficacy outcome. Harms were similar between groups after 48 weeks of treatment, except for a slightly higher proportion of withdrawals due to AEs in the DTG plus RPV group. Bone-related harms, which were of specific interest to patients, and renal-related harms were both unremarkable.

A key limitation of the evidence was the use of an outdated NI margin, which is no longer consistent with current (non-binding) FDA guidance<sup>8</sup> for industry on ARV drug development in HIV infection. Although an attempt was made by the investigators to address the new FDA guidelines by conducting a pre-planned (prior to data freeze) analysis on the proportion of patients classified as “virologic failures,” the fact remains that the original SWORD trials were not designed to specifically evaluate the NI of treatments on the outcome of virologic loss (proportion of patients with HIV-1 RNA  $\geq 50$  copies/mL); testing of this outcome was not controlled for multiplicity. Consequently, it is not possible to conclude whether NI was demonstrated statistically in the SWORD trials on the basis of the new FDA guidance. Nonetheless, the low rates of virologic failure observed, along with the high rates of virologic suppression maintained, suggest that dual therapy is a viable therapeutic option for simplifying the ARV regimen in adult patients previously stabilized on a virologically suppressive triple-ARV regimen. This step-down approach is consistent with guidelines issued by the DHHS.<sup>1</sup>

## Appendix 1: Patient Input Summary

*This section was prepared by CADTH staff based on the input provided by patient groups.*

### 1. Brief Description of Patient Group(s) Supplying Input

The Canadian Treatment Action Council (CTAC) is a non-governmental organization that focuses on access to treatment, care, and support for patients living with HIV and hepatitis C within the country. Their goals are to maintain a dialogue with community members, service providers, policy-makers, and other relevant stakeholders to identify, develop, and implement policy and program solutions. Full CTAC membership is reserved for: individual people living with HIV (including HCV coinfection) and organizations, groups, or projects with a substantial HIV mandate (including HCV coinfection). Associate CTAC membership is open to any individual, organization, group, or project that supports CTAC's mandate and objective.

CTAC has received funding from ViiV Healthcare, the manufacturer of Juluca, in excess of \$50,000 within the past two years. It acknowledges that it has not received any help from outside its patient group to collect or analyze data, or to complete this submission.

### 2. Condition Related Information

The information for this submission is a summary of: a national consultation webinar facilitated by a policy researcher at CTAC; a survey sent on behalf of CTAC via social media to webinar attendees who have had prior exposure to either component within this two-drug combination or to the new combination of dolutegravir plus rilpivirine itself; and survey data collected for a patient submission on dolutegravir, which was used to inform and support this patient submission. In regard to the consultation webinar, all members and organizational partners were invited to participate, and six participants in total were in attendance. In regard to the survey, this was made available to webinar attendees via email between January 10 and 17, 2018, and compiled data from a total of six survey respondents. Of the survey respondents, all were HIV-positive, male, and on treatment for HIV. Five of these respondents reside in Ontario, while one resides in Quebec. Three respondents were in their 50s and three were in their 60s. The number of years in treatment for these respondents varied from five to approximately 34 years.

Many negative mental health outcomes have been associated with those living with HIV, whether as a side effect from treatment or from facing stigma, discrimination, and related stress. One respondent explained how stigma affected both his care and sense of place in his community, saying, *"Life is very health[y] and I do not consider my HIV a disability, although it is a social disability because of the stigma."* Another respondent noted there are also issues with stigma in the medical community: *"Local doctors feel ill-equipped to treat HIV due to inexperience because of low patient caseloads with the condition. Stigma also plays into it I think. Unless they're familiar, doctors still see HIV as something more difficult to live with than it actually is."* Another respondent discussed the challenge of managing HIV while residing in a rural area: *"I live in a rural area and have to travel about 100 km each way for my doctor's appointments. I only see my doctor about every six months. Obviously if I had to travel that far more often it would be a challenge. For those who don't have the support of family this could definitely be an obstacle."*

Respondents all noted substantial impact on caregivers looking after patients living with HIV. One respondent highlighted that the challenges their spouse faces in providing support is surrounding disclosure. According to the respondent, *"hiding from friends and some of*

*our family members that I am HIV-positive” has been extremely difficult and hindered the respondent’s ability to acquire a social safety net. Many of those living with HIV experience intersecting vulnerabilities conditioned by the social determinants of health: the social and structural conditions in which people live, work, and are shaped by the distribution of money, power, and resources. The following stories from webinar respondents were relayed:*

*“My challenges are not treatment-related, but more about how I am treated because I work periodically and I access Trillium [Ontario drug assistance program]. The Trillium plan is a barrier for people who work part-time or periodically. AIDS organizations and the government itself often assume that people will go onto ODSP [Ontario Disability Support Program] or have private drug plans.”*

*“Cost of drugs and Trillium support does not take into account that many people are episodically or precariously employed. Not everyone has a full-time job and not everyone with HIV is on social assistance.”*

### **3. Current Therapy Related Information**

Findings from the survey indicate that from the six respondents who identified as living with HIV, all are currently or have previously been on treatment for their HIV. Their length of time on current therapy ranged from four months to eight years. Considering the survey population was primarily made up of long-term survivors (ranging between 5 to 34 years), this result demonstrates that treatment regimens change somewhat often for people living with HIV. This emphasizes the significant need for the availability of several HIV treatments.

All survey respondents indicated current or past use of regimens containing: darunavir, dolutegravir, emtricitabine, and/or tenofovir. Reported treatment regimens included Prezista (darunavir), Intelence (etravirine), Isentress (raltegravir), Norvir (ritonavir), and/or Atripla (efavirenz/emtricitabine/tenofovir), with different combinations of the above being utilized. None of the respondents to this survey appeared to have had prior or current experience with rilpivirine. Of all the treatments patients reported taking, all noted that their treatment was effective at suppressing their viral load, but one respondent noted there were some side effects experienced that impacted his quality of life. One responded stated, *“When I was diagnosed, I was prescribed Norvir [ritonavir], Truvada [emtricitabine/tenofovir], and Reyataz [atazanavir]. I was extremely sick with AIDS and suffered from leukoencephalopathy. Three months after starting treatment I was undetectable. I went off treatment for a year of my own accord and started again after getting pneumonia. Undetectable again after two months. About three years ago, I switched to Kaletra [lopinavir/ritonavir] on the recommendation of my doctor which kept me undetectable with good CD4 but caused diarrhea, so four months ago I switched to Triumeq [abacavir/dolutegravir/lamivudine]. It is working well: undetectable, CD4 in the 600 range and no side effects.”*

Improvements in quality of life and ability to engage in daily activities with the advent of highly active antiretroviral treatment cannot be overlooked. Discussing the overall impact of treatment on his life, one webinar respondent stated, *“Not only do I feel healthy, I know I am thanks to the regular bloodwork that examines all parameters. Seeing the doctor regularly is a significant benefit of having HIV.”* When asked whether treatment had improved their quality of life, one respondent answered, *“I am very healthy, employed, and also volunteering. Living life fully in a relationship and as a community member.”* Another survey respondent noted that, *“Quality of life has improved because I am not as fatigued as previously.”*



In the webinar consultations, respondents noted staff time, funding, transportation, and other associated costs as barriers to providing support and its impact on treatment adherence, mental health, and other determinants of health. One respondent noted the challenges associated with lack of funding for direct support: *“We have to decrease our direct support services and, in PEI, there are very little services for PHAs (people living with HIV/AIDS) in many areas, including addictions, mental health, housing and food securing, which put treatment lower on the priority list.”* In addition, one respondent noted that difficulties understanding stigma and its impact and navigating HIV-specific social services and institutional systems, including disability, insurance, and mortgage, have presented specific challenges.

#### **4. Expectations About the Drug Being Reviewed**

No survey respondents had experience with the single-dose combination drug dolutegravir/rilpivirine. However, many respondents expressed interest in this combination for benefits in terms of better bone health. One respondent also expressed, *“[I] would be interested in investigating this, as I know my current meds have some effect on the liver and other organs after long-term use.”* Another respondent viewed the potential benefits as less persuasive, saying, *“I don’t see replacing the ‘devil’ I know with the ‘devil’ I don’t know — at least on a personal basis. If I had to make changes — and that time could come since I’ve been on the present regimen for quite some time.”*



## Appendix 2: Literature Search Strategy

### OVERVIEW

Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations <b>Note:</b> Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 24 2018
Alerts:	Bi-weekly search updates until September 20 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

### SYNTAX GUIDE

/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oomezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
Line #	Search String	Results
1	(Juluca* or (rilpivirine* and dolutegravir*)).ti,ab,kf,ot,hw,rn,nm.	408
2	(Rilpivirin* or edurant* or TMC278 or TMC 278 or R278474 or R 278474 or HSDB 8153 or HSDB8153).ti,ab,kf,ot,hw,rn,nm.	2403
3	(500287-72-9 or FI96A8X663).rn,nm.	1651
4	2 or 3	2403
5	(dolutegravir* or tivica* or gsk 1349572 or gsk1349572 or gsk 572 or gsk572 or s 1349572 or s1349572 or s 349572 or s349572).ti,ab,kf,ot,hw,rn,nm.	1981
6	(1051375-19-9 or 1Q1V9V5WYQ).rn,nm.	1102
7	5 or 6	1981
8	4 and 7	410
9	1 or 8	410
10	9 use medall	64
11	dolutegravir plus rilpivirine/	15
12	(Juluca* or (rilpivirine* and dolutegravir*)).ti,ab,kw.	159
13	11 or 12	164
14	*rilpivirine/	464
15	(Rilpivirin* or edurant* or TMC278 or TMC 278 or R278474 or R 278474 or HSDB 8153 or HSDB8153).ti,ab,kw.	1359
16	14 or 15	1382
17	*dolutegravir/	472
18	(dolutegravir* or tivica* or gsk 1349572 or gsk1349572 or gsk 572 or gsk572 or s 1349572 or s1349572 or s 349572 or s349572).ti,ab,kw.	1404
19	17 or 18	1421
20	16 and 19	164
21	13 or 20	169
22	21 use oemez	107
23	conference abstract.pt.	2868621
24	22 not 23	69
25	10 or 24	133
26	remove duplicates from 25	74

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

**Grey Literature**

Dates for Search:	January 2018
Keywords:	Juluca, rilpivirine, dolutegravir
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (<https://www.cadth.ca/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

## Appendix 3: Excluded Studies

**Table 11: Excluded Studies**

Reference	Reason for Exclusion
40	Editorial
41	(DEXA study) — substudy of select subgroup of patients in pivotal trials
2	Review article
42	Study design
43	Editorial
38	Study design
44	Study design
45	Population
46	Clinical practice guideline
47	Review article
48	Study design

## Appendix 4: Detailed Outcome Data

**Table 12: Patients Without Virologic Data — Early-Switch Phase**

Virologic Efficacy Outcomes	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
<b>No virologic data, N (%), ITT-E</b>	10 (4)	9 (4)	14 (5)	11 (4)	24 (5)	20 (4)
• Discontinued study due to AE or death	5 (2)	2 (< 1)	12 (5)	1 (< 1)	17 (3)	3 (< 1)
• Discontinued study for other reasons	5 (2)	7 (3)	2 (< 1)	9 (4)	7 (1)	16 (3)
• Missing data during window but on study	0	0	0	1 (< 1)	0	1 (< 1)

AE = adverse event; cAR = current antiretroviral regimen; DTG = dolutegravir; ITT-E = intention-to-treat exposed; RPV = rilpivirine.

Source: SWORD-1 Clinical Study Report (Table 15-18, 2.040).

**Table 13: Proportion of Patients With Plasma HIV-1 RNA Below 50 Copies/mL at Week 48 by Subgroups — Snapshot Analysis (ITT-E)**

Subgroup	SWORD-1		SWORD-2		Pooled	
	DTG + RPV	cAR	DTG + RPV	cAR	DTG + RPV	cAR
<b>Biological sex</b>						
<i>Female</i>						
N	58	51	62	57	120	108
Number responded (%)	53 (91)	46 (90)	58 (94)	52 (91)	111 (93)	98 (91)
Difference in proportion (95% CI) <sup>a</sup>	1.2 (-9.7 to 12.1)		2.3 (-7.2 to 11.9)		1.8 (-5.5 to 9.0)	
<i>Male</i>						
N	194	205	199	198	393	403
Number responded (%)	187 (96)	199 (97)	188 (94)	188 (95)	375 (95)	387 (96)
Difference in proportion (95% CI) <sup>a</sup>	-0.7 (-4.2 to 2.8)		-0.5 (-4.9 to 3.9)		-0.6 (-3.4 to 2.2)	
<i>P</i> value for test of homogeneity <sup>b</sup>	0.752		0.605		0.550	
<b>Baseline ARV third-agent class</b>						
<i>Protease inhibitor</i>						
N	75	74	58	62	133	136
Number responded (%)	71 (95)	68 (92)	53 (91)	60 (97)	124 (93)	128 (94)
Difference in proportion (95% CI) <sup>a</sup>	2.8 (-5.3 to 10.8)		-5.4 (-13.9 to 3.1)		-0.9 (-6.7 to 4.9)	
<i>Non-nucleoside reverse transcriptase inhibitor</i>						
N	131	134	144	144	275	278
Number responded (%)	124 (95)	131 (98)	139 (97)	134 (93)	263 (96)	265 (95)
Difference in proportion (95% CI) <sup>a</sup>	-3.1 (-7.71 to 0.5)		3.5 (-1.6 to 8.6)		0.3 (-3.1 to 3.8)	
<i>Integrase strand transfer inhibitor</i>						

Subgroup	SWORD-1		SWORD-2		Pooled	
	DTG + RPV	cAR	DTG + RPV	cAR	DTG + RPV	cAR
N	46	48	59	49	105	97
Number responded (%)	45 (98)	46 (96)	54 (92)	46 (94)	99 (94)	92 (95)
Difference in proportion (95% CI) <sup>a</sup>	2.0 (-5.1 to 9.0)		-2.4 (-12.1 to 7.4)		-0.6 (-6.8 to 5.7)	
P value for test of homogeneity <sup>b</sup>	0.317		0.179		0.930	

ARV = antiretroviral; cAR = current antiretroviral regimen; CI = confidence interval; DTG = dolutegravir; ITT-E = intention-to-treat exposed; RNA = ribonucleic acid; RPV = rilpivirine.

<sup>a</sup> Difference = proportion on DTG minus proportion on cAR (unadjusted).

<sup>b</sup> One-sided P value from weighted least squares chi-squared statistic. A P value ≤ 0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Source: SWORD-1 Clinical Study Report (Table 24, 27, 2.053, 2.763), SWORD-2 (Table 24, 28).

**Table 14: Other Efficacy Outcomes — Early-Switch Phase**

Other Efficacy Outcomes	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
<b>CD4+ count, cells/mm<sup>3</sup></b>						
Baseline, median (IQR)	611.5 (442 to 800)	638.0 (459.5 to 846.0)	609.0 (467.0 to 814.0)	628.0 (481.0 to 824.0)	611.0 (459.0 to 809.0)	638.0 (470.0 to 829.0)
N (%)	239 (95)	245 (96)	245 (94)	241 (95)	484 (94)	486 (95)
Change from baseline to week 48, median (IQR)	25.0 (-68 to 119)	35.0 (-37.0 to 104.0)	29.0 (-47.0 to 108.0)	13.0 (-59.0 to 108.0)	28.0 (-55.0 to 112.5)	22.0 (-46.0 to 108.0)
<b>Development of drug resistance</b>						
CVW, N (%)	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)
Resistance by drug class for patients with CVW	INSTI <sup>a</sup>	none	NNRTI <sup>b</sup>	none	INSTI, <sup>a</sup> NNRTI <sup>b</sup>	none
PVW, N (%)	1 (< 1)	0	0	2 (< 1)	1 (< 1)	2 (< 1)
<b>EQ-5D-5L</b>						
N (%)	252 (100)	254 (99)	257 (98)	251 (98)	509 (99)	505 (99)
<b>Utility score</b>						
Baseline, mean (SE)	0.946 (0.0057)	0.936 (0.0071)	0.963 (0.0048)	0.951 (0.0056)	0.955 (0.0037)	0.943 (0.0045)
Change from baseline to week 48, mean <sup>c</sup> (SE)	0.000 (0.0052)	-0.003 (0.0052)	-0.006 (0.0053)	-0.004 (0.0054)	-0.003 (0.0037)	-0.004 (0.0037)
Difference versus cAR (CI)	0.004 (-0.011 to 0.018)		-0.002 (-0.017 to 0.013)		0.001 (-0.009 to 0.011)	
P value	0.603		0.821		0.847	
<b>VAS score</b>						
Baseline, mean (SE)	88.1 (0.68)	87.6 (0.79)	89.9 (0.63)	87.5 (0.71)	89.0 (0.47)	87.5 (0.53)
Change from baseline to week 48, mean <sup>c</sup> (SE)	3.776 (0.5565)	2.990 (0.5543)	1.944 (0.5811)	2.860 (0.5881)	2.857 (0.4012)	2.919 (0.4028)
Difference versus cAR (CI)	0.786 (-0.759 to 2.332)		-0.917 (-2.548 to 0.715)		-0.063 (-1.180 to 1.055)	
P value	0.318		0.270		0.913	

Other Efficacy Outcomes	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
<b>Regimen adherence by VAS</b>						
Baseline score, mean (SD)	98.3 (4.3)	98.5 (3.3)	98.4 (3.2)	98.3 (3.7)	98.4 (3.8)	98.4 (3.5)
Change from baseline to week 48, mean (SD)	-0.47 (3.9)	-0.25 (3.6)	-0.54 (4.5)	0.05 (4.2)	-0.50 (4.2)	-0.10 (3.9)
N (%)	240 (95)	245 (96)	245 (94)	238 (93)	485 (95)	483 (95)

cAR = current antiretroviral regimen; CI = confidence interval; CVW = confirmed virologic withdrawal; DTG = dolutegravir; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; INSTI = integrase strand transfer inhibitor; IQR = interquartile range; NNRTI = non-nucleoside reverse transcriptase inhibitor; PP = per-protocol; PVW = precautionary virologic withdrawal; RPV = rilpivirine; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

ITT-exposed analysis set.

<sup>a</sup> This particular mutation was present at baseline and did not affect susceptibility to DTG.

<sup>b</sup> This mutation did not affect susceptibility to RPV.

<sup>c</sup> Adjusted for age, baseline third agent, gender, race, and baseline VAS score.

Source: SWORD-1 Clinical Study Report (Tables 15, 16, 17, 18), SWORD-2 Clinical Study Report.

**Table 15: Adverse Events in Five Per Cent or More of Patients — Early-Switch Phase**

Adverse Events, n (%)	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
Any TEAE	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)
Nasopharyngitis	28 (11)	28 (11)	21 (8)	22 (9)	49 (10)	50 (10)
Headache	23 (9)	17 (7)	18 (7)	6 (2)	41 (8)	23 (5)
Upper respiratory tract infection	7 (3)	10 (4)	17 (7)	27 (11)	24 (5)	37 (7)
Diarrhea	21 (8)	16 (6)	11 (4)	11 (4)	32 (6)	27 (5)
Back pain	9 (4)	19 (7)	6 (2)	12 (5)	15 (3)	31 (6)
Bronchitis	7 (3)	5 (2)	16 (6)	10 (4)	23 (4)	15 (3)
Influenza	4 (2)	13 (5)	10 (4)	4 (2)	14 (3)	17 (3)
Arthralgia	8 (3)	4 (2)	13 (5)	5 (2)	21 (4)	9 (2)

cAR = current antiretroviral regimen; DTG = dolutegravir; RPV = rilpivirine; TEAE = treatment-emergent adverse event.

Source: SWORD-1 Clinical Study Report (Table 3.080).

**Table 16: Serious Adverse Events — Early-Switch Phase**

Adverse Events, n (%)	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
Any SAE	9 (4)	12 (5)	18 (7)	9 (4)	27 (5)	21 (4)
<b>Infections and infestations</b>						
Any event	2 (< 1)	6 (2)	8 (3)	0	10 (2)	6 (1)
Pneumonia	1 (< 1)	0	2 (< 1)	0	3 (< 1)	0
Abscess limb	0	0	1 (< 1)	0	1 (< 1)	0
Bronchitis	0	1 (< 1)	0	0	0	1 (< 1)
Gastroenteritis	1 (< 1)	0	0	0	1 (< 1)	0
Hepatitis C	0	1 (< 1)	0	0	0	1 (< 1)
Influenza	0	1 (< 1)	0	0	0	1 (< 1)

Adverse Events, n (%)	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
Lymphogranuloma venereum	0	0	1 (< 1)	0	1 (< 1)	0
Orchitis	0	0	1 (< 1)	0	1 (< 1)	0
Periorbital cellulitis	0	0	1 (< 1)	0	1 (< 1)	0
Peritonsillar abscess	0	1 (< 1)	0	0	0	1 (< 1)
Pulmonary sepsis	0	0	1 (< 1)	0	1 (< 1)	0
Rectal abscess	0	1 (< 1)	0	0	0	1 (< 1)
Rotavirus infection	0	0	1 (< 1)	0	1 (< 1)	0
Thyroglossal cyst infection	0	1 (< 1)	0	0	0	1 (< 1)
<b>Injury, poisoning, and procedural complications</b>						
Any event	1 (< 1)	0	3 (1)	3 (1)	4 (< 1)	3 (< 1)
Alcohol poisoning	0	0	1 (< 1)	0	1 (< 1)	0
Facial bones fracture	0	0	1 (< 1)	0	1 (< 1)	0
Fibula fracture	0	0	0	1 (< 1)	0	1 (< 1)
Foreign body	0	0	0	1 (< 1)	0	1 (< 1)
Joint injury	0	0	0	1 (< 1)	0	1 (< 1)
Tibia fracture	0	0	1 (< 1)	0	1 (< 1)	0
Wrist fracture	1 (< 1)	0	0	0	1 (< 1)	0
<b>Gastrointestinal disorders</b>						
Any event	1 (< 1)	2 (< 1)	2 (< 1)	0	3 (< 1)	2 (< 1)
Anal fistula	0	1 (< 1)	0	0	0	1 (< 1)
Gastrointestinal hemorrhage	0	0	1 (< 1)	0	1 (< 1)	0
Gastroesophageal reflux disease	0	0	1 (< 1)	0	1 (< 1)	0
Pancreatitis acute	1 (< 1)	0	0	0	1 (< 1)	0
Proctitis	0	1 (< 1)	0	0	0	1 (< 1)
<b>Neoplasms —benign, malignant, and unspecified (including cysts and polyps)</b>						
Any event	2 (< 1)	2 (< 1)	1 (< 1)	0	3 (< 1)	2 (< 1)
Breast cancer	0	1 (< 1)	0	0	0	1 (< 1)
Hodgkin's disease mixed cellularity stage unspecified	1	0	0	0	1 (< 1)	0
Kaposi sarcoma	0	0	1 (< 1)	0	1 (< 1)	0
Lung neoplasm malignant	0	1 (< 1)	0	0	0	1 (< 1)
Plasmablastic lymphoma	1 (< 1)	0	0	0	1 (< 1)	0
<b>Psychiatric disorders</b>						
Any event	1 (< 1)	0	2 (< 1)	1 (< 1)	3 (< 1)	1 (< 1)
Suicide attempt	0	0	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
Depression	0	0	1 (< 1)	0	1 (< 1)	0
Panic attack	1 (< 1)	0	0	0	1 (< 1)	0
<b>Ear and labyrinth disorders</b>						
Any event	1 (< 1)	0	0	1 (< 1)	1 (< 1)	1 (< 1)
Tympanic membrane perforation	0	0	0	1 (< 1)	0	1 (< 1)
Vertigo	1 (< 1)	0	0	0	1 (< 1)	0
<b>Eye disorders</b>						
Any event	0	0	0	2 (< 1)	0	2 (< 1)
Keratitis	0	0	0	1 (< 1)	0	1 (< 1)
Retinal detachment	0	0	0	1 (< 1)	0	1 (< 1)



Adverse Events, n (%)	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
<b>Hepatobiliary disorders</b>						
Any event	1 (< 1)	0	1 (< 1)	0	2 (< 1)	0
Cholecystitis chronic	0	0	1 (< 1)	0	1 (< 1)	0
Drug-induced liver injury	1 (< 1)	0	0	0	1 (< 1)	0
<b>Musculoskeletal and connective tissue disorders</b>						
Any event	0	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)
Hemarthrosis	0	0	1 (< 1)	0	1 (< 1)	0
Intervertebral disc protrusion	0	1 (< 1)	0	0	0	1 (< 1)
<b>Nervous system disorders</b>						
Any event	0	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)
Headache	0	0	1 (< 1)	0	1 (< 1)	0
Toxic encephalopathy	0	1 (< 1)	0	0	0	1 (< 1)
<b>Renal and urinary disorders</b>						
Any event	0	0	2 (< 1)	0	2 (< 1)	0
Acute kidney injury	0	0	1 (< 1)	0	1 (< 1)	0
Renal colic	0	0	1 (< 1)	0	1 (< 1)	0
<b>Respiratory, thoracic, and mediastinal disorders</b>						
Any event	0	0	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
Eosinophilic pneumonia acute	0	0	1 (< 1)	0	1 (< 1)	0
Pulmonary embolism	0	0	0	1 (< 1)	0	1 (< 1)
<b>General disorders and administration site conditions</b>						
Any event	0	1 (< 1)	0	0	0	1 (< 1)
Non-cardiac chest pain	0	1 (< 1)	0	0	0	1 (< 1)
<b>Immune system disorders</b>						
Any event	0	0	0	1 (< 1)	0	1 (< 1)
Drug hypersensitivity	0	0	0	1 (< 1)	0	1 (< 1)
Jarisch–Herxheimer reaction	0	0	0	1 (< 1)	0	1 (< 1)

cAR = current antiretroviral regimen; DTG = dolutegravir; RPV = rilpivirine; SAE = serious adverse event.

Source: SWORD-1 Clinical Study Report (Table 3.160).

**Table 17: Withdrawals Due to Adverse Events — Early-Switch Phase**

Adverse Events, n (%)	SWORD-1		SWORD-2		Pooled	
	DTG + RPV (n = 252)	cAR (n = 256)	DTG + RPV (n = 261)	cAR (n = 255)	DTG + RPV (n = 513)	cAR (n = 511)
Any WDAE	9 (4)	2 (< 1)	12 (5)	1 (< 1)	21 (4)	3 (< 1)
<b>Psychiatric disorders</b>						
Any event	4 (2)	0	5 (2)	1 (< 1)	9 (2)	1 (< 1)
Anxiety	2 (< 1)	0	2 (< 1)	0	4 (< 1)	0
Depression	1 (< 1)	0	2 (< 1)	0	3 (< 1)	0
Insomnia	1 (< 1)	0	1 (< 1)	0	2 (< 1)	0
Depressed mood	0	0	1 (< 1)	0	1 (< 1)	0
Panic attack	1 (< 1)	0	0	0	1 (< 1)	0
Suicidal ideation	0	0	1 (< 1)	0	1 (< 1)	0
Suicide attempt	0	0	0	1 (< 1)	0	1 (< 1)
<b>Gastrointestinal disorders</b>						
Any event	3 (1)	0	4 (2)	0	7 (1)	0
Abdominal distension	1 (< 1)	0	1 (< 1)	0	2 (< 1)	0
Dyspepsia	0	0	2 (< 1)	0	2 (< 1)	0
Gastrointestinal hemorrhage	0	0	1 (< 1)	0	1 (< 1)	0
Pancreatitis, acute	1 (< 1)	0	0	0	1 (< 1)	0
Peptic ulcer	1 (< 1)	0	0	0	1 (< 1)	0
<b>Neoplasms — benign, malignant, and unspecified (including cysts and polyps)</b>						
Any event	2 (< 1)	2 (< 1)	1 (< 1)	0	3 (< 1)	2 (< 1)
Breast cancer	0	1 (< 1)	0	0	0	1 (< 1)
Hodgkin's disease, mixed cellularity, stage unspecified	1 (< 1)	0	0	0	1 (< 1)	0
Kaposi sarcoma	0	0	1 (< 1)	0	1 (< 1)	0
Lung neoplasm, malignant	0	1 (< 1)	0	0	0	1 (< 1)
Plasmablastic lymphoma	1 (< 1)	0	0	0	1 (< 1)	0
<b>Nervous system disorders</b>						
Any event	0	0	2 (< 1)	0	2 (< 1)	0
Headache	0	0	1 (< 1)	0	1 (< 1)	0
Tremor	0	0	1 (< 1)	0	1 (< 1)	0
<b>Hepatobiliary disorders</b>						
Any event	1 (< 1)	0	0	0	1 (< 1)	0
Drug-induced liver injury	1 (< 1)	0	0	0	1 (< 1)	0
<b>Respiratory, thoracic, and mediastinal disorders</b>						
Any event	0	0	1 (< 1)	0	1 (< 1)	0
Eosinophilic pneumonia, acute	0	0	1 (< 1)	0	1 (< 1)	0

cAR = current antiretroviral regimen; DTG = dolutegravir; RPV = rilpivirine; WDAE = withdrawal due to adverse event.

Source: SWORD-1 Clinical Study Report (Table 3.230).

## Appendix 5: Summary of Bioequivalence of Dolutegravir Plus Rilpivirine Co-Formulation Versus Individual Formulations

### Aim

To summarize the details and findings of one phase I, bioequivalency study 201676.<sup>49</sup>

### Findings

#### Study Characteristics

The manufacturer conducted one phase I study to evaluate the bioequivalence of the fixed-dose combination (co-formulation) of dolutegravir 50 mg and rilpivirine 25 mg and the co-administration of its two single-entity components in the moderate-fat fed state in healthy adult volunteers (Table 18). For this study, each enrolled patient was randomized to receive either a single dose of the dolutegravir 50 mg/rilpivirine 25 mg fixed-dose combination, or dolutegravir 50 mg plus rilpivirine 25 mg as single entities under moderate-fat fed conditions.<sup>49</sup>

**Table 18: Study Characteristics of Bioequivalence Study**

Description	201676
Study design	Phase I, open-label, randomized, two-way crossover, bioequivalence
Test therapy	DTG 50 mg/ RPV 25 mg FDC (moderate-fat fed)
Reference therapy	Co-administration of Tivicay (DTG 50 mg) tablet and Edurant (RPV 25 mg) (moderate-fat fed)

DTG = dolutegravir; FDC = fixed-dose combination; RPV = rilpivirine.

Source: Clinical Study Report for 201676.<sup>49</sup>

#### Study Formulations

In this study, the formulations designed to be compared were a fixed-dose combination of dolutegravir 50 mg/rilpivirine 25 mg with the co-administration of two single-entity components dolutegravir 50 mg (Tivicay) and rilpivirine 25 mg (Edurant).<sup>49</sup>

#### End Points

The primary end point of this study was area under the concentration-time curve of the analyte in plasma over the time interval from zero extrapolated to infinity ( $AUC_{0-\infty}$ ) and maximum measured concentration of the analyte in plasma ( $C_{max}$ ) for both dolutegravir and rilpivirine, as seen in Table 19.

This study used  $AUC_{0-\infty}$  and  $C_{max}$  to compare the bioequivalence of the fixed-dose tablet to that of the co-administration of the separate tablet formulations of dolutegravir 50 mg and rilpivirine 25 mg in a moderately fed state. This study was meant to comply with bioequivalence standards outlined by Health Canada, which recommends that the  $C_{max}$  and  $AUC_{0-\infty}$  be within 80.0% and 125.0%, inclusive.<sup>50</sup> Safety and tolerability parameters were also included in this study, which included a change from baseline in vital signs (such as

blood pressure and heart rate), number of subjects with adverse events, toxicity grading of clinical laboratory tests, and a change from baseline in 12-lead electrocardiogram.<sup>49</sup>

**Table 19: Study Characteristics of Bioequivalence Studies**

End Point	Description
<b>Primary end points</b>	
AUC <sub>0-∞</sub>	Area under the concentration-time curve of the analyte in plasma over the time interval from zero extrapolated to infinity
C <sub>max</sub>	Maximum measured concentration of the analyte in plasma
<b>Secondary and other end points</b>	
AUC <sub>0-tl</sub>	Area under the concentration-time curve of the analyte in plasma over the time interval from zero to the time of the last quantifiable data point
C <sub>24</sub>	Observed concentration at 24 hours post-dose
t <sub>max</sub>	Time from dosing to the maximum concentration of the analyte in plasma
t <sub>1/2</sub>	Terminal half-life of the analyte in plasma

Source: Clinical Study Reports for 201676.<sup>49</sup>

### Study Populations

The final sample size used in this study was 118 healthy adult patients. The majority of the population were young, white males; however, there was a proportion of those of black or African-American descent represented in this population. A total of 118 patients were randomized within this study. A total of 113 subjects completed both treatment periods during the study.<sup>49</sup>

**Table 20: Population Characteristics and Patient Disposition of Bioequivalence Study**

	201676
<b>Number of patients, N</b>	<b>118</b>
Male, n (%)	82 (69)
Age in years, mean (SD)	30.7 (9.46)
White, n (%)	82 (69)
Black or African-American, n (%)	30 (25)
BMI in kg/m <sup>2</sup> , mean (SD)	26.21 (3.31)
<b>Patient disposition</b>	
Number of patients planned (n)	118
Number of patients randomized	118
Number of patients included in PK parameter summary population, n (%)	113 (96)
Number of patients completed as planned, n (%)	113 (96)
Number of patients withdrawn (any reason), n (%)	5 (4)
Physician decision to withdrawal, n (%)	2 (2)
Patient withdrew consent, n (%)	3 (3)

PK = pharmacokinetics; SD = standard deviation.

Source: Clinical Study Reports for 201676.<sup>49</sup>

### Pharmacokinetic Results

Table 21 summarizes the key results from the bioequivalence study.<sup>49</sup> Across this trial, the geometric means and corresponding 95% confidence intervals for the dolutegravir/rilpivirine fixed-dose combination were within the 80% to 125% boundary criteria used by Health Canada to assess bioequivalence.<sup>51</sup>

**Table 21: Key Results in Pharmacokinetic Parameters**

Parameter	Treatment (n = 113)	Geometric Mean (CVb%)	95% CI	Geometric Mean Ratios (%; 95% CI)
<b>Dolutegravir</b>				
<b>AUC<sub>0-∞</sub></b> (h*ug/mL)	FDC	65.0 (24.9)	(62.1 to 68.0)	1.037 (1.010 to 1.064)
	DTG 50 mg + RPV 25 mg	62.7 (25.3)	(59.8 to 65.6)	
<b>C<sub>max</sub></b> (ug/mL)	FDC	3.65 (18.2)	(3.53 to 3.77)	1.050 (1.022 to 1.078)
	DTG 50 mg + RPV 25 mg	3.47 (18.8)	(3.36 to 3.60)	
<b>AUC<sub>0-tl</sub></b> (h*ug/mL)	FDC	63.6 (25.2)	(60.7, 66.6)	1.038 (1.011, 1.066)
	DTG 50 mg + RPV 25 mg	61.3 (25.6)	(58.5, 64.2)	
<b>C<sub>24</sub></b> (ug/mL)	FDC	1.00 (30.6)	(0.949, 1.06)	1.045 (1.012, 1.078)
	DTG 50 mg + RPV 25 mg	0.958 (29.8)	(0.907, 1.01)	
<b>Rilpivirine</b>				
<b>AUC<sub>0-∞</sub></b> (h*ug/mL)	FDC	3.25 (42.8)	(3.02, 3.51)	1.108 (1.046, 1.175)
	DTG 50 mg + RPV 25 mg	2.93 (43.7)	(2.71, 3.17)	
<b>C<sub>max</sub></b> (ug/mL)	FDC	0.0933 (42.2)	(0.0866, 0.101)	1.124 (1.047, 1.207)
	DTG 50 mg + RPV 25 mg	0.0830 (38.2)	(0.0775, 0.0890)	
<b>AUC<sub>0-tl</sub></b> (h*ug/mL)	FDC	3.06 (41.6)	(2.84, 3.30)	1.107 (1.042, 1.176)
	DTG 50 mg + RPV 25 mg	2.77 (43.4)	(2.56, 2.99)	
<b>C<sub>24</sub></b> (ug/mL)	FDC	0.0312 (37.6)	(0.0292, 0.0334)	1.101 (1.034, 1.173)
	DTG 50 mg + RPV 25 mg	0.0284 (40.6)	(0.0264, 0.0305)	

AUC<sub>0-∞</sub> = area under the concentration-time curve of the analyte in plasma over the time interval from zero extrapolated to infinity; AUC<sub>0-tl</sub> = area under the concentration-time curve of the analyte in plasma over the time interval from zero to the last measurable time point; C<sub>24</sub> = drug concentration at 24 hours post-dose; CI = confidence interval; C<sub>max</sub> = maximum concentration of the analyte; CVb% = within-subject coefficients of variation; DTG = dolutegravir; FDC = dolutegravir 50 mg/rilpivirine 25 mg fixed-dose combination; RPV = rilpivirine.

Source: Clinical Study Reports for 201676.<sup>49</sup>

### Conclusions

Two phase I studies demonstrated that the dolutegravir/rilpivirine fixed-dose combination is bioequivalent to the individual components administered separately, based on commonly accepted criteria.<sup>51</sup>

## Appendix 6: Summary of Late-Switch Phase in SWORD-1 and SWORD-2 Trials

### Aim

To summarize the data from the late-switch phase (i.e., 52 to 148 weeks) of the SWORD-1 and SWORD-2 trials.

### Findings

#### Study Design

The late-switch phase of the SWORD-1 and SWORD-2 trials began after week 52. Patients initially randomized to continue their current, three-drug antiretroviral regimen (cAR) during weeks 0 to 48 with confirmed virologic suppression at week 48, were switched to dual therapy with dolutegravir (DTG) plus rilpivirine (RPV) during weeks 48 to 52. Patients initially randomized to DTG plus RPV during weeks 0 to 48 continued their dual-therapy regimen without interruption from week 48 to week 148. Both groups — early-switch and late-switch — were now taking DTG plus RPV for a maximum cumulative follow-up of 148 weeks. The late-switch phase of the SWORD trials is ongoing. A request to the manufacturer for the most current data cut-off yielded a limited data set covering up to week 100.<sup>39</sup>

#### Population Demographics and Baseline Disease Characteristics

There were no population demographics or baseline disease characteristics presented for patients participating in the late-switch SWORD trials.

#### Intervention

For the late-switch phase (week 52 to week 148), all patients were taking DTG plus RPV. There was no comparator group.

#### Outcomes

The manufacturer provided a limited, descriptive, pooled data set, which included the proportion of patients with HIV-1 RNA below 50 copies/mL at week 100 and the proportion of patients with virologic non-response at week 100 using snapshot algorithm and the intention-to-treat exposed (ITT-E) population in both instances. Topline safety data are also presented (Table 22).

#### Results

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Conclusion**

The data provided from the late-switch phase are limited. Without more supportive data, it is difficult to say with certainty whether these data provide evidence of durable virologic suppression.

**Table 22: Efficacy and Key Safety Results at Week 100 for SWORD Trials (Pooled), ITT-E**

Outcomes	DTG + RPV		
	Early-Switch Group		Late-Switch Group
	Day 1 to Week 48	Day 1 to Week 100	Week 52 to Week 100
Randomized and exposed, N	[REDACTED]	[REDACTED]	[REDACTED]
<b>Efficacy, n (%)</b>			
Virologic success	[REDACTED]	[REDACTED]	[REDACTED]
Virologic non-response	[REDACTED]	[REDACTED]	[REDACTED]
No virologic data	[REDACTED]	[REDACTED]	[REDACTED]
Due to one of the following:			
• Discontinued due to AE or death	[REDACTED]	[REDACTED]	[REDACTED]
• Discontinued for other reasons	[REDACTED]	[REDACTED]	[REDACTED]
• Missing data during window but on study	[REDACTED]	[REDACTED]	[REDACTED]
<b>Key safety,<sup>b</sup> n (%)</b>			
WDAEs	[REDACTED]	[REDACTED]	[REDACTED]
SAEs	[REDACTED]	[REDACTED]	[REDACTED]

AE = adverse event; cAR = current antiretroviral regimen; CVW = confirmed virologic withdrawal; DTG = dolutegravir; ITT-E = intention-to-treat exposed; RPV = rilpivirine; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

<sup>a</sup> Only patients who were virologically suppressed at week 48 entered the late-switch phase. As a result, 34 (7%) of patients from the cAR group were excluded.

<sup>b</sup> These results are based on the safety population who received ≥ 1 dose of DTG plus RPV and represent all safety data available in the database at the time of the data cut-off.

Source: Supplemental data provided by manufacturer;<sup>39</sup> SWORD-1 Clinical Study Report.

## Appendix 7: Summary of DEXA Substudy

### Aim

To summarize the details and findings of one substudy of the phase III SWORD-1 and SWORD-2 studies, 202094 (DEXA).<sup>37</sup>

### Findings

#### Study Design

This was a substudy of the open-label, parallel-group SWORD-1 and SWORD-2 RCTs designed to evaluate whether switching to a dolutegravir plus rilpivirine regimen was associated with a difference in bone health in adult patients infected with HIV-1. The study design, populations, treatments, and outcomes are summarized in Table 23.

Patients who were participants in SWORD-1<sup>10</sup> or SWORD-2<sup>11</sup> receiving a stable antiretroviral regimen containing tenofovir disoproxil fumarate (TDF) prior to randomization were eligible for this substudy. As part of the SWORD-1<sup>10</sup> and SWORD-2<sup>11</sup> studies, patients were randomized 1:1 to receive open-label dolutegravir 50 mg plus rilpivirine 25 mg once daily or continue with their TDF-based antiretroviral therapy through week 48. Randomization was stratified by a baseline third-agent class (integrase strand transfer inhibitor [INSTI], non-nucleoside reverse transcriptase inhibitor [NNRTI], or protease inhibitor [PI]), age group (< or ≥ 50 years old), and planned participation in the substudy.

#### Population Demographics and Baseline Disease Characteristics

Demographic and baseline disease characteristics for patients who participated in this substudy are described in Table 24.

The substudy population included all participants who were registered in the substudy and received at least one dose of dolutegravir plus rilpivirine or their TDF-based cAR. The outcome of interest in this study was a percentage change from baseline to week 48 in total hip bone mineral areal density. The target study enrolment was ≥ 100 patients, with a goal of about 150 patients. Assuming a true population effect of a 1.9% treatment difference with a standard deviation (SD) of 3.5%, a sample size of 100 participants provided 77% power for demonstrating a statistically significant percentage change in this outcome.

#### Intervention

Patients who were selected to participate in the substudy underwent dual-energy X-ray absorptiometry (DXA) scans to assess bone mineral density (BMD). These tests were performed on all substudy participants at baseline and at week 48 or upon withdrawal.

DXA scans which assessed BMD were performed using non-DOS-based GE Lunar or Hologic scanners on day 1 (baseline) and at week 48 or at the withdrawal visit and read centrally by the DXA vendor located in Durham, North Carolina. The vendor was blinded to the treatment arm of study participants.

#### Outcomes

The primary end point was percentage change from baseline to week 48 in total hip BMD (as areal density in g/cm<sup>2</sup>), which included femoral neck, trochanter, and intertrochanteric



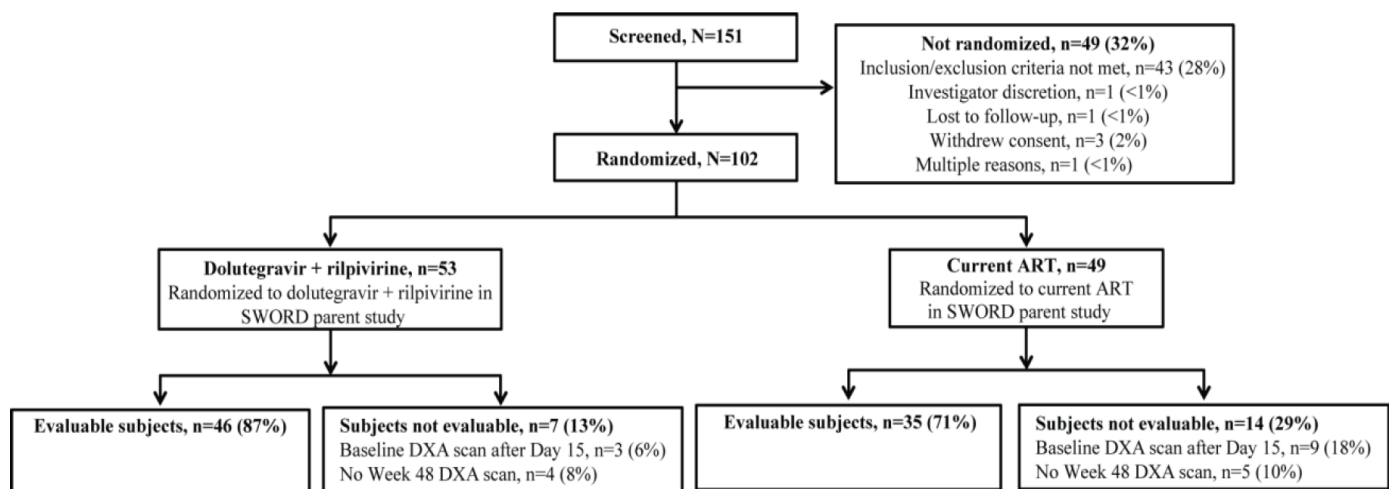
areas. The key secondary end point was percentage change from baseline to week 48 in lumbar spine (L1 to L4) BMD assessed as areal density in g/cm<sup>2</sup>. Additional secondary end points were change from baseline to week 48 in total hip and lumbar spine BMD assessed as areal density, T-scores, and z scores by baseline third-agent class (INSTI, NNRTI, PI). The T-score and z scores are both derived from the mean and standard deviation of the reference population. T-scores depict the difference in bone mass compared with that of an average healthy 30-year-old adult.<sup>52</sup> The T-score is a standard deviation from the mean, equivalent to a 10% to 12% difference in bone mass.<sup>52</sup> Osteoporosis has been defined as a T-score that is 25% lower than the average healthy 30-year-old adult, or a T-score lower than -2.5. A z score is determined similarly to a T-score, except that the reference population was age-matched to the normal population.<sup>52</sup> Significant differences observed in baseline characteristics were adjusted for via an analysis of covariance (ANCOVA) model.

This study assessed only adverse events that were related to the DXA scan procedure.

### Patient Disposition and Exposure

Of 151 patients screened, 49 failed screening based on either inclusion/exclusion criteria, investigator discretion, lost to follow-up, withdrawal of consent, or multiple reasons. Participant disposition is displayed in Figure 3.

**Figure 3: Disposition of Patients in DEXA Substudy**



ART = antiretroviral therapy; DXA = dual-energy X-ray absorptiometry.

Source: Clinical Study Report.<sup>37</sup>

A total of 102 patients were enrolled in this substudy, with 53 patients evaluated in the dolutegravir plus rilpivirine group and 49 patients in the TDF-based antiretroviral therapy (ART) group. Of these, 12 patients (dolutegravir plus rilpivirine, 3; TDF-based cAR, 9) had baseline DXA scans outside the protocol-defined time window (i.e., after day 15) and thus were excluded from the evaluable population. A further 8 patients (dolutegravir plus rilpivirine, 4; TDF-based cAR, 4) discontinued during the early-switch phase in the parent study and, therefore, did not undergo week 48 DXA scans. In addition, one patient from the TDF-based cAR arm switched to dolutegravir plus rilpivirine on the day of the week 48 scan; hence, the scan was excluded from the analysis. Therefore, 81 patients (dolutegravir

plus rilpivirine, n = 46; TDF-based cAR, n = 35) had evaluable DXA scans at baseline and week 48. Patients were considered evaluable if they had a DXA scan result available at both baseline and week 48. Therefore, 81 patients overall had DXA scans which fulfilled these requirements and were therefore included in the week 48 analysis. Participant demographics are shown in Table 24.

Approximately half of the participants in both treatment groups were female, with a slightly higher median age belonging to the group of patients on TDF-based cAR, as well as a slightly higher percentage of those with an age equal to or above 50 years. The majority of patients in both groups reported they were non-smokers and did not consume alcohol, and there was a slightly higher proportion of patients in the dolutegravir plus rilpivirine group who were non-smokers and did not consume alcohol. Most patients in both treatment arms had normal total hip and lumbar spine T-scores; however, the mean baseline BMD scores for total hip and lumbar spine were slightly higher in the TDF-based cAR group compared with the dolutegravir plus rilpivirine group. Less than 30% were classified as osteopenic, and no patients met the osteoporosis criterion by total hip T-score. Finally, there were higher numbers of patients in the TDF-based cAR group who did not undergo baseline bone densitometry, which reduced the number of patients in this group who were able to be evaluated for the primary end point in this study.

Table 23: Details of DEXA Substudy<sup>37</sup>

		DEXA <sup>37</sup>
DESIGNS & POPULATIONS	<b>Study Design</b>	Phase III, multi-centre, multi-national, open-label, parallel-group
	<b>Locations</b>	32 sites in 6 countries (Argentina, Belgium, Canada, Spain, UK, US)
	<b>Number of Participants (N)</b>	102
	<b>Inclusion Criteria</b>	Patients participating in SWORD-1 <sup>10</sup> or SWORD-2 <sup>11</sup> receiving a stable antiretroviral therapy containing TDF prior to randomization
	<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• ≤ 3 vertebrae in the L1 to L4 range suitable for BMD measurement</li> <li>• Bilateral hip replacement</li> <li>• Uncontrolled thyroid disease</li> <li>• Male hypogonadism</li> <li>• Endocrine diseases</li> <li>• Fragility fracture history</li> <li>• Severe osteoporosis (indicated by prior DXA scan-derived T-score of -3.5 or lower)</li> <li>• BMI &lt; 18kg/m<sup>2</sup> or ≥ 40kg/m<sup>2</sup></li> <li>• 25-hydroxy vitamin D &lt; 15ng/mm<sup>3</sup> (37.5nmol/mm<sup>3</sup>)</li> <li>• Current use of or intent to initiate tamoxifen, bone-related treatment, or anabolic steroids (except for testosterone if received at a stable dose for the last 6 months before entry and with no plan to discontinue during the study)</li> <li>• Treatment with or intent to initiate anticonvulsant therapy or other hormonal therapy, unless given for at least 6 months before study entry</li> </ul>
	<b>Objective</b>	To evaluate changes at week 48 in bone mineral density after switching from an antiretroviral regimen containing TDF to dolutegravir plus rilpivirine
EXPOSURE	<b>Intervention</b>	Dolutegravir 50 mg plus rilpivirine 25 mg versus TDF-based cAR
	<b>Duration</b>	48 weeks
OUTCOMES	<b>Main End Point(s)</b>	Percentage change from baseline to week 48 in total hip BMD (g/cm <sup>2</sup> )
	<b>Other End Points</b>	Total hip and lumbar spine BMD assessed as T-scores and z scores by baseline third-line agent (INSTI, NNRTI, PI)
NOTES	<b>Publications</b>	Clinical Study Report (SWORD DEXA substudy) <sup>37</sup>

BMD = bone mineral density; BMI = body mass index; cAR = current antiretroviral regimen; DXA = dual-energy X-ray absorptiometry; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate.

Source: Clinical Study Reports.<sup>10,11,37</sup>

**Table 24: Patient Demographics and Baseline Characteristics**

	Dolutegravir + Rilpivirine (n = 53 <sup>a</sup> )	TDF-Based ART (n = 49 <sup>a</sup> )
Age, median (min, max)	43.0 (21, 62)	46.0 (22, 76)
≥ 50 years, n (%)	15 (28)	16 (33%)
Female, n (%)	27 (51)	26 (53)
White race, n (%)	44 (83)	40 (82)
Baseline BMI, mean (SD) [min, max], kg/m <sup>2</sup>	25.2 (3.9) [18.7, 33.3]	25.8 (4.8) [18.9, 38.7]
Baseline CD4+ lymphocyte count, n (%), ≥ 500 cells/mm <sup>3</sup>	31 (58)	33 (67)
<b>Baseline third-agent class, n (%)</b>		
NNRTI	32 (60)	33 (67)
INSTI	9 (17)	5 (10)
PI	12 (23)	11 (22)
<b>History of smoking at baseline, n (%)</b>		
Never / not a current smoker	40 (75)	36 (73)
< 1 pack-year <sup>b</sup>	10 (19)	8 (16)
≥ 1 pack-year <sup>b</sup>	3(6)	5(10)
<b>Alcohol consumption at baseline,<sup>c</sup> n (%)</b>		
No alcohol consumption	37 (70)	30 (61)
< 14 units per week	15 (28)	17 (35)
≥ 14 units per week	1 (2)	2 (4)
<b>Baseline BMD, n, mean (SD) g/cm<sup>2</sup></b>		
Total hip	N = 50, 0.964 (0.1457)	N = 40, 0.974 (0.1146)
Lumbar spine	N = 52, 1.063 (0.1613)	N = 42, 1.086 (0.1495)
<b>Baseline BMD, n, mean (SD) T-score</b>		
Total hip	N = 50, -0.348 (1.10)	N = 40, -0.306 (0.841)
Lumbar spine	N = 52, -0.688 (1.204)	N = 42, -0.625 (1.226)
<b>Baseline BMD, n, mean (SD) z score</b>		
Total hip	N = 49, -0.071 (1.045)	N = 40, -0.011 (0.872)
Lumbar spine	N = 52, -0.220 (1.219)	N = 42, -0.168 (1.301)
<b>Total hip T-score, n (%)</b>	N = 50	N = 40
Normal (> -1)	36 (72)	32 (80)
Osteopenia (-2.5 to ≤ -1)	14 (28)	8 (20)
Osteoporosis (≤ -2.5)	0	0
Mean total hip T-score	-0.348	-0.306
<b>Lumbar spine T-score, n (%)</b>	N = 52	N = 42
Normal (> -1)	29 (56)	26 (62)
Osteopenia (-2.5 to ≤ -1)	20 (38)	14 (33)
Osteoporosis (≤ -2.5)	3 (6)	2 (5)
Mean lumbar spine T-score	-0.071	-0.011

ART = antiretroviral therapy; BMD = bone mineral density; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SD = standard deviation; TDF = tenofovir disoproxil fumarate.

<sup>a</sup> Unless otherwise noted.

<sup>b</sup> A pack-year is defined as 20 cigarettes (a pack) smoked every day for a year.

<sup>c</sup> A unit of alcohol is one half-pint of beer, one glass of wine, or one short measure of spirits.

Source: Clinical Study Report.<sup>37</sup>

### Safety

Results from the primary analysis showed a statistically significant increase in total hip BMD from baseline to week 48 as assessed by areal density for subjects who switched to dolutegravir plus rilpivirine compared with subjects who continued on treatment with an antiretroviral regimen containing TDF. This statistically significant increase in total hip BMD was supported by greater increases in T-scores and z scores from baseline to week 48 for those patients switched to dolutegravir plus rilpivirine compared with those on a TDF-containing regimen. In addition, compared with those patients continuing their TDF-based cAR, statistically significant improvements in BMD in the lumbar spine for the dolutegravir plus rilpivirine group by g/cm<sup>2</sup>, T-score, and z score were reported (Table 25).

**Table 25: Comparison of Change in Bone Mineral Density From Baseline to 48 Weeks**

	Dolutegravir + Rilpivirine		TDF-Based ART		Difference in Adjusted Percentage Between Groups (95% CI) <sup>a</sup>	P Value <sup>a</sup>
	Baseline	Week 48	Baseline	Week 48		
<b>Total Hip BMD</b>						
<b>Areal density (g/cm<sup>2</sup>)</b>						
N	50	46	40	35		
Mean BMD at baseline <sup>d</sup> and mean adjusted <sup>a</sup> difference from baseline at week 48 (SD)	0.964 (0.146)	+0.012 (0.023)	0.974 (0.115)	+0.000 (0.017)		
Mean adjusted percentage change from baseline at week 48, % (95% CI) <sup>a</sup>		+1.34 (0.68 to 2.01)		+0.05 (-0.71 to 0.82)	+1.29 (0.27 to 2.31)	<b>0.014</b>
<b>T-score</b>						
N	50	46	40	35		
Mean BMD at baseline and mean adjusted <sup>a</sup> difference from baseline at week 48, T-score, (SD)	-0.348 (1.110)	+0.094 (0.172)	-0.306 (0.841)	+0.002 (0.126)		
Mean adjusted percentage change from baseline at week 48, % (95% CI) <sup>a</sup>		+0.09 (0.05 to 0.14)		+0.01 (-0.05 to 0.06)	+0.09 (0.02 to 0.16)	<b>0.016</b>
<b>Z score</b>						
N	49	46	40	35		
Mean BMD at baseline and mean adjusted <sup>a</sup> difference from baseline at week 48, z score, (SD)	-0.071 (1.045)	0.108 (0.177)	-0.011 (0.872)	-0.023 (0.123)		
Mean adjusted percentage change from baseline at week 48, % (95% CI) <sup>a</sup>		+0.11 (0.06 to 0.15)		+0.02 (-0.03 to 0.08)	+0.08 (0.01 to 0.15)	<b>0.026</b>
<b>Lumbar spine BMD</b>						
<b>Areal density (g/cm<sup>2</sup>)</b>						
N	52	46	42	35		
Mean BMD at baseline and mean adjusted <sup>a</sup> difference from baseline at week 48, areal density, g/cm <sup>2</sup> (SD)	1.063 (0.161)	0.015 (0.030)	1.09 (0.150)	0.000 (0.032)		
Mean adjusted percentage change from baseline at week 48, % (95% CI) <sup>a</sup>		+1.46 (0.65 to 2.28)		+0.15 (-0.79 to 1.09)	+1.32 (0.07 to 2.57)	<b>0.039</b>

	Dolutegravir + Rilpivirine		TDF-Based ART		Difference in Adjusted Percentage Between Groups (95% CI) <sup>a</sup>	P Value <sup>a</sup>
	Baseline	Week 48	Baseline	Week 48		
<b>T-score</b>						
N	52	46	42	35		
Mean BMD at baseline <sup>a</sup> and mean adjusted <sup>a</sup> difference from baseline at week 48, T-score, g/cm <sup>2</sup> (SD)	-0.688 (1.204)	0.130 (0.259)	-0.625 (1.226)	0.003 (0.269)		
Mean adjusted percentage change from baseline at week 48, % (95% CI) <sup>a</sup>		+0.13 (0.05 to 0.20)		+0.01 (-0.08 to 0.10)	+0.12 (0.00 to 0.23)	<b>0.049</b>
<b>Z score</b>						
N	52	46	42	35		
Mean BMD at baseline <sup>a</sup> and mean adjusted <sup>a</sup> difference from baseline at week 48, z score, g/cm <sup>2</sup> (SD)	-0.220 (1.219)	0.174 (0.262)	-0.168 (1.301)	0.019 (0.265)		
Mean adjusted percentage change from baseline at week 48, % (95% CI) <sup>a</sup>		+0.17 (0.09, 0.25)		+0.02 (-0.07, 0.11)	+0.15 (0.03, 0.27)	<b>0.013</b>

ANCOVA = analysis of covariance; ART = antiretroviral therapy; BMD = bone mineral density; BMI = body mass index; CI = confidence interval; DXA = dual-energy X-ray absorptiometry; SD = standard deviation; TDF = tenofovir disoproxil fumarate-based therapy.

Note: Items in bold indicate significance.

<sup>a</sup> Estimates and associated P values are from an ANCOVA model adjusted for baseline BMD value, T-score/z score value, age at study entry, and baseline BMI.

<sup>b</sup> A total of 21 patients were excluded from the BMD analyses; 7 patients in the dolutegravir and rilpivirine group and 14 patients in the TDF-based ART group. These patients did not have evaluable BMD data at both baseline and week 48 because they either had their baseline DXA scans (or rescans) after day 15 or did not have week 48 DXA scans in the early-switch phase of the parent study.

Source: Clinical Study Report.<sup>37</sup>

## Adverse Events

Adverse events planned for collection were those considered by the investigator to be specifically attributable to the DXA scan procedure. As of the data cut-off date, November 22, 2016, there were no adverse events or serious adverse events of this nature reported during this substudy.

## Limitations

There are issues with the design of the study that limit its interpretation. Firstly, there is an unequal percentage of evaluable patients between the study arms. There is an observed difference at baseline for values of BMD in hip and lumbar spine, with a slightly lower overall value of BMD in patients who had been switched to dolutegravir plus rilpivirine. This difference was adjusted for in the ANCOVA analysis when assessing outcomes; however, an effect on overall results cannot be ruled out. Secondly, the sample size for the outcome of interest in this study was smaller than the goal of 150 patients, due to a number of patients not meeting the inclusion criteria and the fact that a proportion of patients recruited for this study did not have evaluable BMD within 15 days of baseline or at 48 weeks. The latter could have introduced selection bias for the patients included in the final analysis who may be more adherent to study medications and protocol. Furthermore, the two groups were not prognostically balanced due to a slightly higher age, and a more substantial smoking and alcohol history at baseline in the group continuing TDF-based cAR. Finally,

the measurement uncertainty value in the process of BMD measurements for the device used was not reported, which may play a factor in change in results.

With respect to external validity, the timeline of this study was over a course of 46 to 48 weeks from baseline to final BMD measurements, which is considered a short duration when measuring changes in BMD over time. Furthermore, DXA scans are not typically conducted in this patient population when they are asymptomatic due to the fact that it is not considered clinically relevant. In addition, BMD is a surrogate for the more clinically relevant outcome of fracture; fracture incidence was not measured in the DEXA substudy.

It has been reported previously in literature that the detrimental effect of certain ART regimens (including TDF-based regimens) on BMD has been reported to slightly decrease and stabilize after one or two years.<sup>51</sup> As a result, it is difficult to determine whether the small, albeit statistically significant increase in percentage BMD values will translate into a relevant clinical benefit overall.

## Summary

The objective of this DEXA substudy was to obtain data on whether there is any change in BMD in total hip and lumbar spine following a switch from a TDF-based cAR to a dual therapy of dolutegravir plus rilpivirine. Compared with those continuing treatment with a TDF-based cAR, there was a statistically significant percentage increase in BMD observed in the total hip at 48 weeks in the primary analysis; similarly, there was a greater percentage increase in BMD at the lumbar spine after 48 weeks in patients switched to dolutegravir plus rilpivirine compared with TDF-based cAR (uncertain control of multiplicity). However, it is questionable whether the increases observed in BMD are clinically relevant. The clinical expert consulted by CDR noted that the changes observed in this study have limited clinical relevance. However, due to the fact that this is intended as lifelong therapy, he was encouraged by the potential for a reduction or improvement in long-term bone-related complications. As of the planned cut-off period of 48 weeks, there were no adverse events reported in this study, defined as events considered by an investigator to be attributable to the DEXA scan procedure. This study is limited by its short duration, and the resultant failure to detect clinically important between-treatment differences in terms of bone-related complications such as fractures.

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