

CADTH COMMON DRUG REVIEW

# Clinical Review Report

**Doravirine (Pifeltro)**

**(Merck Canada Inc.)**

**Indication:** Doravirine (Pifeltro) is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine.

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## Abbreviations

<b>3TC</b>	lamivudine
<b>BIC</b>	bictegravir
<b>AE</b>	adverse event
<b>ABC</b>	abacavir
<b>ART</b>	antiretroviral therapy
<b>ARV</b>	antiretroviral
<b>CI</b>	confidence interval
<b>CTAC</b>	Canadian Treatment Action Council
<b>DB</b>	double-blind
<b>DHHS</b>	US Department of Health and Human Services
<b>DTG</b>	dolutegravir
<b>DOR</b>	doravirine
<b>DRV</b>	darunavir
<b>DRV/r</b>	ritonavir-boosted darunavir
<b>DSG</b>	delayed switch group
<b>EFV</b>	efavirenz
<b>EVG</b>	elvitegravir
<b>EQ-5D-5L</b>	EuroQol 5-Dimensions 5-Levels questionnaire
<b>FAS</b>	full-analysis set
<b>FDC</b>	fixed-dose combination
<b>FTC</b>	emtricitabine
<b>HDL</b>	high-density lipoprotein cholesterol
<b>IDC</b>	indirect comparison
<b>InSTI</b>	integrase strand transfer inhibitor
<b>ISG</b>	immediate switch group
<b>IVRS/IVWS</b>	interactive voice/Web response system
<b>LDL</b>	low-density lipoprotein cholesterol
<b>MCID</b>	minimal clinically important difference
<b>NIM</b>	noninferiority margin
<b>NMA</b>	network meta-analysis
<b>NNRTI</b>	non-nucleoside reverse transcriptase inhibitor
<b>NRTI</b>	nucleoside reverse transcriptase inhibitor
<b>OL</b>	open-label
<b>PDVF</b>	protocol-defined virologic failure
<b>PI</b>	protease inhibitor
<b>PP</b>	per-protocol

<b>RCT</b>	randomized controlled trial
<b>RAM</b>	resistance-associated mutation
<b>RNA</b>	ribonucleic acid
<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>ULN</b>	upper limit of normal
<b>WDAE</b>	withdrawal due to adverse event

<b>Drug</b>	Doravirine (Pifeltro)
<b>Indication</b>	Pifeltro (doravirine) is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine
<b>Reimbursement Request</b>	As per indication
<b>Dosage Form(s)</b>	100 mg tablet
<b>NOC Date</b>	October 12, 2018
<b>Manufacturer</b>	Merck Canada Inc.

## Executive Summary

### Introduction

HIV is responsible for causing a condition that gradually weakens the immune system.<sup>1</sup> HIV is transmitted via body fluids such as blood, semen, genital secretions, and breast milk; most commonly from unprotected sexual intercourse or through sharing of contaminated needles and syringes with an infected person.<sup>2</sup> Left untreated, HIV infection can progress to AIDS and ultimately death. Surveillance data from the Public Health Agency of Canada estimates that there were approximately 84,409 people in Canada living with HIV/AIDS at the end of 2016, with an incidence rate of 6.4 per 100,000 population, or 2,344 new reported cases.<sup>3</sup> Antiretroviral (ARV) treatments have improved steadily since the invention of highly active forms of antiretroviral therapy (ART) in the mid-1990s, and the availability of newer and potent combination therapies. Treatments are aimed at lowering the level of HIV in the body, thereby allowing the immune system to recover and respond to other infections. Newer ARTs have significantly reduced HIV-associated morbidity and mortality and HIV is largely considered a manageable chronic condition.<sup>4</sup>

According to the US Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*, ARV regimens for treatment-naive patients generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic enhancer (booster) (cobicistat or ritonavir).<sup>4</sup> The goals of ARV regimens are: maximally and durably suppress plasma HIV ribonucleic acid (RNA) below detectable limits (< 50 copies/mL); restore and preserve immunologic function (increase CD4 cell counts); reduce HIV-associated morbidity; prolong the duration and quality of survival; and prevent HIV transmission. For treatment-experienced patients with viral suppression, the DHHS guidelines recommend selecting a new ARV regimen based on patients' previous ART history, including virologic responses, past ART-associated toxicities and intolerances, resistance-test results, drug-drug interactions, and pill burden, in addition to other non-clinical considerations.<sup>4</sup>

Current ARTs are not curative; they require lifelong administration and high levels of adherence to ensure achievement of treatment goals. To simplify ARV regimens for patients and support long-term adherence, several single-tablet regimens (STRs) are available, alongside other non-STRs, providing clinicians and patients with an array of therapeutic



options. Doravirine (DOR; 100 mg) is an NNRTI of HIV-1. NNRTIs act by binding to and blocking HIV reverse transcriptase (an enzyme that is essential to the HIV replication cycle), thereby preventing HIV from replicating. The Health Canada–recommended dose is one 100 mg tablet taken orally once daily with or without food.

## Indication under review

PIFELTRO (doravirine) is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine.

## Reimbursement criteria requested by sponsor

As per indication

The objective of this systematic review was to evaluate the beneficial and harmful effects of doravirine, in combination with other ARV medicinal products, for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to DOR.

## Results and Interpretation

### Included Studies

Three randomized, active-controlled, noninferiority trials met the inclusion criteria for this systematic review: two double-blind (DB) trials (DRIVE-FORWARD, N = 769<sup>5,6</sup> and DRIVE-AHEAD, N = 728<sup>7,8</sup>) conducted in treatment-naïve patients; and one open-label (OL) trial (DRIVE-SHIFT, N = 673<sup>9</sup>) conducted in virologically suppressed patients on a stable ARV regimen. The DB and OL trials had a total follow-up duration of 96 weeks and 48 weeks, respectively. Treatments administered in the DB trials were DOR or ritonavir-boosted darunavir (DRV/r), each given in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC) (in DRIVE-FORWARD), and DOR/3TC/TDF or efavirenz/FTC/TDF (EFV/FTC/TDF) (in DRIVE-AHEAD). In DRIVE-SHIFT, patients either immediately switched to DOR/3TC/TDF to be received for 48 weeks (immediate switch group, ISG) or continued their baseline regimen for 24 weeks (consisting of a ritonavir- or cobicistat-boosted PI, or cobicistat-boosted INSTI, or NNRTI, each administered with two NRTIs) before switching to DOR/3TC/TDF (delayed switch group, DSG). The primary efficacy outcome in all trials was virologic suppression defined as HIV-1 RNA < 50 copies/mL (calculated using the FDA snapshot algorithm; all missing data were treated as failures regardless of the reasons). In DRIVE-FORWARD and DRIVE-AHEAD the between-treatment differences for the primary efficacy outcome were analyzed at week 48, while in DRIVE-SHIFT the primary analysis compared the proportion of patients maintaining HIV-1 RNA < 50 copies/mL in the ISG group at 48 weeks versus the DSG group at 24 weeks (on baseline regimen). The noninferiority margin (NIM) for the primary outcome was 10% and 8% for the DB and OL trials, respectively. Subgroup analyses were conducted to assess the effect of baseline HIV-1 RNA (< versus ≥ 100,000 copies/mL) on virologic suppression in treatment-naïve patients. Secondary end points included changes in lipid levels and neuropsychiatric adverse events (AEs). Baseline patient characteristics and medical and treatment histories were largely similar between-treatment groups. The majority of the patients were male, with a mean age of 26 to 32 years (treatment-naïve) and 43 years (treatment-experienced/switch). Across the trials, approximately 20% to 23% had > 100,000 HIV-1 RNA copies/mL (treatment-naïve trials only), 9% to 18% had a history of AIDS, less than 5% had hepatitis B and/or C, and 2% to 7% took lipid-lowering therapy.

Limitations noted in the two DB trials are as follows. The comparators used in DRIVE-FORWARD and DRIVE-AHEAD, namely DRV/r and EFV, are less commonly used in a treatment-naive setting according to DHHS guidelines. The clinical expert consulted for this review agreed this is also the case in the Canadian context. Older ARV drugs such as EFV and darunavir are known to be associated with negative neuropsychiatric and gastrointestinal events. DOR may therefore demonstrate a favourable neuropsychiatric and gastrointestinal profile compared with EFV and darunavir, respectively. Among treatment-naive patients, the rate of discontinuation ranged between 13% and 19% at week 48, and between 18% and 29% at week 96 across trials. Notably, the discontinuation rate was higher in the comparator arms than in the DOR arms. Given that those who discontinued the study (including those who discontinued due to AEs) were considered not to have achieved the primary outcome, the comparative efficacy of DOR may be overestimated.

Several important methodological limitations were noted in the switch trial (DRIVE-SHIFT). First, the primary end point used in the switch trial was not consistent with the latest FDA recommendations for HIV drugs. According to the recommendations, the primary efficacy outcome for switch trials should be HIV-1 RNA  $\geq$  50 copies/mL, as the end point is focused on patients who lose virologic control as a result of switching from a stable, virologically suppressive regimen to another regimen. However, DRIVE-SHIFT was initiated before the new recommendations were published. For the primary efficacy end point, the NIM chosen for DRIVE-SHIFT (8%) was more stringent than the 10% recommended by the FDA, which was used in DRIVE-FORWARD and DRIVE-AHEAD. However, there is some uncertainty regarding whether the 8% NIM for the primary outcome in DRIVE-SHIFT was actually met, as the FDA snapshot algorithm to account for missing data (missing data = failure) was not followed properly. Instead, some patients with missing data at week 48 had their blood samples reanalyzed from other sources and the data were added to the analyses dataset post hoc. Following this modification, the NIM was met for the primary efficacy outcome. However, noninferiority was not initially demonstrated with the true FDA snapshot approach. Finally, analysis of the primary end point was based on an unequal period of exposure to the respective study drugs (DOR/3TC/TDF or baseline regimens). Patients in the ISG arm received DOR for 48 weeks whereas those in the DSG arm received their baseline regimens for 24 weeks followed by DOR/3TC/TDF for 24 weeks. Statistical comparisons were not made between the treatment arms at week 24 for most end points (including the primary efficacy end point), or were not controlled for multiplicity. Instead, results for the ISG arm at week 48 were compared with the DSG arm at week 24 in many cases.

## Efficacy

All efficacy analyses were conducted in the full-analysis set, a modified intention-to-treat population that consisted of all randomized patients who received at least one dose of the study medication and had at least one measurement of the outcome (baseline or post-baseline).

Among treatment-naive patients, the primary outcome (proportion of patients with HIV-1 RNA  $<$  50 copies/mL at week 48) was achieved by 83.8% and 79.9% patients receiving DOR and DRV/r in DRIVE-FORWARD, respectively; and by 84.3% and 80.8% patients receiving DOR/3TC/TDF and EFV/FTC/TDF in DRIVE-AHEAD, respectively. The between-treatment differences in the two trials were 3.9% (95% confidence interval [CI], -1.6 to 9.4) and 3.5% (95% CI, -2.0 to 9.0), respectively. In both cases, the pre-specified NIM of 10% was met, as the lower bounds of the 95% CI for treatment differences were above -10 percentage points. Per-protocol analyses supported the conclusion of noninferiority. The

proportions of patients with virologic success at week 96 were 73.1% and 66.0% for patients receiving DOR and DRV/r in DRIVE-FORWARD, respectively; and 77.5% and 73.6% for patients receiving DOR/3TC/TDF and EFV/FTC/TDF in DRIVE-AHEAD, respectively. Results from the subgroup analyses indicated a lower virologic success rate in patients with baseline plasma HIV-1 RNA > 100,000 copies/mL compared with those having HIV-1 RNA ≤ 100,000 copies/mL in both DRIVE-FORWARD and DRIVE-AHEAD.

The proportion of treatment-naive patients with HIV-1 RNA ≥ 50 copies/mL (virologic failure) at week 48 using the FDA-defined snapshot approach was similar in both trials' treatment arms: 11.2% versus 13.1% for DOR and DRV/r, respectively, in DRIVE-FORWARD, and 10.7% versus 10.2% for DOR/3TC/TDF and EFV/FTC/TDF, respectively, in DRIVE-AHEAD. No formal statistical testing was conducted. The proportion of patients with HIV-1 RNA ≥ 50 copies/mL at 96 weeks was 17.2% versus 20.2% for DOR and DRV/r, respectively, in DRIVE-FORWARD, and 15.1% versus 12.1% for DOR/3TC/TDF and EFV/FTC/TDF in DRIVE-AHEAD.

In DRIVE-SHIFT, the proportion of patients with HIV-1 RNA < 50 copies/mL was 90.8% at week 48 in the ISG group compared with 94.6% in the DSG group at week 24, with a treatment difference of -3.8% (95% CI, -7.9 to 0.3). Given the lower bound of the 95% CI was not less than -8%, switching to DOR/3TC/TDF was considered noninferior to continued treatment with baseline regimen. However, DRIVE-SHIFT had a number of methodological issues leading to questionable validity with respect to establishing comparative efficacy between switching to DOR/3TC/TDF versus staying on baseline regimens. The comparison of virologic suppression between groups based on different durations of follow-up is unusual and the CADTH Common Drug Review team is uncertain of the impact this had on the results. Between-treatment comparisons based on the same duration of follow-up would have been more internally valid. The between-treatment difference for the proportion of patients with HIV-1 RNA < 50 copies/mL at the same time point in each group (24 weeks) was -0.9% (95%CI, -4.7 to 3.0); statistical testing did not control for multiplicity. Further, based on guidance from the FDA, the appropriate end point for treatment-switch trials is the proportion of patients with HIV-1 RNA ≥ 50 copies/mL with an associated NIM of 4%. The proportions of patients with HIV-1 RNA ≥ 50 copies/mL were similar between the ISG and DSG at weeks 48 and 24 (1.6% and 1.8% respectively), and between the ISG and DSG at week 24 for each group (1.8% in both groups); between-treatment differences were -0.2 (95% CI, -2.5 to 2.1) and 0.0 (95%CI, -2.3 to 2.3), respectively. However, statistical testing was not controlled for multiplicity.

Among other efficacy end points, CD4 cell counts increased from baseline in all patients, irrespective of treatment arms, time points, and trials. However, between-treatment differences within trials did not reach statistical significance in any case. Resistance to any of the study medications occurred infrequently. Among patients who completed each trial, adherence to treatment was generally high, with most patients (> 85%) reporting an adherence rate of 90% or more. However, it should be noted that the overall adherence among all participants is likely lower when study discontinuation is taken into account. Health-related quality of life was assessed by the visual analogue scale of the EuroQol 5-Dimensions 5-Levels questionnaire in DRIVE-SHIFT only. The mean change from baseline between the ISG and DSG arm was -0.76 and -0.86 at week 48, respectively, and -1.23 and -0.7 at week 24, respectively. Between-treatment difference for the latter time point was -0.54 (95% CI, -3.07 to 2.00).

## Harms

The frequency of AEs at week 96 was similar between the treatment arms in the DB trials: 84.6% versus 82.8% among patients receiving DOR and DRV/r, respectively, in DRIVE-FORWARD, and 88.2% versus 93.1% among patients receiving DOR and EFV, respectively, in DRIVE-AHEAD. In the switch trial, 80.3% of patients in the ISG arm receiving DOR through week 48 experienced AEs. A higher proportion of treatment-switch patients receiving DOR reported AEs at week 24. This pattern is consistent with the notion that patients switching therapies are likely to experience more AEs than those remaining on their baseline therapy: 68.9% versus 52.5% among patients receiving DOR and baseline regimens, respectively; and 60.3% of patients in the DSG arm experienced AEs post-switching between week 24 and 48.

Among treatment-naïve patients, serious adverse events (SAEs) were reported by 5% to 7% of patients who received DOR, and approximately 8% of those who received DRV/r or EFV. Among treatment-switch patients, 1% to 5% of patients across treatment arms reported SAEs. The proportions of patients who withdrew from the study due to adverse events (WDAEs) were generally low, ranging from 1% to 7% in treatment-naïve patients and 0% to 4% in treatment-switch patients. A total of 13 deaths were reported in the three trials, one of which (cause of death: myocardial infarction; patient was in DRIVE-SHIFT and receiving DOR) was attributed to the study drug, although no confirmatory diagnosis (by a medical professional or autopsy) was done.

DOR showed an improvement in lipid profiles among treatment-naïve and switch patients at all time points. Two of the five measured lipid parameters were tested with adjustment for multiplicity, fasting low-density lipoprotein cholesterol (LDL), and non-high-density lipoprotein cholesterol (HDL). In DRIVE-FORWARD and DRIVE-AHEAD, fasting LDL and non-HDL levels were decreased in the DOR arms and increased in their respective comparator arms at week 48 in DRIVE-FORWARD and DRIVE-AHEAD; the mean differences for change from baseline in fasting LDL between the treatment arms were -14.6 mg/dL (-18.1 to -11.1) and -10.0 mg/dL (-13.5 to -6.5), respectively;  $P < 0.0001$  in both cases. For change from baseline in non-HDL, the mean differences between the treatment arms were -19.3 mg/dL (95% CI, -23.3 to -15.3) and -17.02 mg/dL (95% CI, -20.9 to -13.2), respectively, with a  $P$  value  $< 0.0001$  in both cases. Among treatment-switch patients, those in the ISG had a numerically greater decrease from baseline in fasting LDL and non-HDL at week 24 compared with the DSG; the mean difference was -15.3 (95% CI, -18.9 to -1.6) and -23.9 (95% CI, -28.1 to -19.6), respectively; no  $P$  value was reported in either case.

DOR was associated with fewer neuropsychiatric AEs. However, the benefits were largely seen in comparison with EFV in DRIVE-AHEAD, which is commonly associated with neuropsychiatric side effects. Statistical superiority of DOR over EFV was shown for three categories of neuropsychiatric AEs at week 48 in DRIVE-AHEAD: dizziness, sleep disorders and disturbances, and altered sensorium, with between-treatment differences of -28.3 (95% CI, -34.0 to -22.5), -13.5 (95% CI, -19.1 to -7.9), and -3.8 (95% CI, -7.6 to -0.3), respectively. Data for hepatic enzymes, cardiovascular disease, renal and bone-related toxicity, and skin disorders did not show any notable benefits in favour of or against DOR regimens or any of the comparator regimens.

### Indirect Treatment Comparison

The manufacturer-submitted network meta-analysis (NMA) suggests that, with respect to virologic success (HIV-1 RNA < 50 copies/mL) [REDACTED]

[REDACTED]

[REDACTED] The NMA did not provide adequate information on the statistical analyses plan to assess the validity of the results and NMA assumptions. The missing information, coupled with the small network size, the failure to assess NMA assumptions, and the differences in trial design and the definition used for protocol-defined virologic failure to determine virologic response, translate to a high degree of uncertainty in the presented efficacy and safety results. Other limitations include the limited scope of the manufacturer-submitted indirect comparison (IDC), where only interventions relevant to their economic model in treatment-naive patients were analyzed, without assessing relevant comparators such as [REDACTED]

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

Doravirine, an NNRTI, has some positive attributes compared with the predecessors in its class, including a lack of neuropsychiatric side effects (compared with efavirenz), a lack of a requirement to be taken with food and with normal gastric acidity (unlike rilpivirine), and once-daily dose (unlike etravirine).

Its role will be limited by its late entry into the market. As a single daily-dose “third component” of an ARV combination, it has been preceded to market by rilpivirine, dolutegravir, and DRV/r, among others. As a co-formulated STR, Delstrigo (DOR/3TC/TDF) is one of almost a dozen available single-tablet options, including Atripla (and generics), Complera, Odefsey, Stribild, Genvoya, Triumeq, Biktarvy, Symtuza, and Juluca.

The most commonly prescribed antivirals for treatment-naive patients, or those switching for reasons of convenience or tolerance, are the SRTs, in particular Genvoya and Triumeq. Although each has its own idiosyncracies, most are well tolerated, convenient, and effective. The use of the DOR STR would be infrequent, as the tenofovir component of the Delstrigo STR is the TDF formulation, which is associated with renal and bone toxicities. The newer tenofovir alafenamide formulation, found in Biktarvy and Genvoya, is not associated with these side effects and is generally preferred by prescribing physicians.

As a single component of a regimen, DOR (Pifeltro) would be a reasonable treatment consideration if an STR is not available or an option for a patient. Most likely, it would be used where a tenofovir-containing regimen is not considered ideal, and where side effects of Triumeq have occurred. It would most likely be used with Kivexa (or its generic counterpart). Its use is anticipated to be infrequent.

<sup>a</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.

## Conclusions

Results from two DB randomized controlled trials in treatment-naive patients demonstrate that DOR is noninferior to DRV/r when given in combination with FTC/TDF or ABC/3TC, and that DOR/3TC/TDF is noninferior to EFV/FTC/TDF in achieving virologic suppression (HIV-1 RNA < 50 copies/mL) at week 48. Differential study discontinuation in both trials may have biased the estimates of comparative efficacy toward DOR and DOR/3TC/TDF, but the impact is unlikely to change the conclusion of noninferiority. DOR and DOR/3TC/TDF resulted in a more favourable lipid profile (LDL and non-HDL) compared with DRV/r and EFV/FTC/TDF, respectively, and DOR/3TC/TDF was associated with fewer neuropsychiatric events compared with EFV/FTC/TDF, a combination known for its neuropsychiatric effects due to its EFV component. The manufacturer-submitted IDC of ARVs in [REDACTED] did not include a number of relevant comparators (such as [REDACTED]). Furthermore, the IDC suffered from methodologic limitations that resulted in a high degree of uncertainty in the estimates of comparative efficacy and safety between [REDACTED].

Results from one OL randomized controlled trial in virologically suppressed, treatment-experienced patients suggest that DOR/3TC/TDF is noninferior to continuing baseline treatment (consisting of a ritonavir- or cobicistat-boosted PI, cobicistat-boosted InSTI, or NNRTI, each administered with two NRTIs) based on the primary outcome of HIV-1 RNA < 50 copies/mL. However, this finding is of questionable validity given the two treatment arms had an unequal period of exposure to the respective study drugs. Additionally, the FDA-recommended end point of interest for switch trials (HIV-1 RNA  $\geq$  50 copies/mL) was not included in the statistical hierarchy. Results for secondary outcomes included in the statistical hierarchy (LDL and non-HDL) provide support for a favourable impact of DOR/3TC/TDF on patients' lipid profiles.

**Table 1: Summary of Results**

Outcome	DRIVE-FORWARD		DRIVE-AHEAD		DRIVE-SHIFT	
	DOR N = 383	DRV/r N = 383	DOR/3TC/TDF N = 364	EFV/FTC/TDF N = 364	ISG week 0 to 48 N = 447	DSG week 0 to 24 N = 223
<b>HIV-1 RNA &lt; 50 copies/mL at week 48, n (%)<sup>a</sup></b>						
n (%)	321 (83.8)	306 (79.9)	307 (84.3)	294 (80.8)	406/447 (90.8)	211/223 (94.6)
Difference % (95% CI)	3.9 (-1.6 to 9.4) NI met <sup>b</sup>		3.5 (-2.0 to 9.0) NI met <sup>b</sup>		-3.8 (-7.9 to 0.3) NI met <sup>b</sup>	
<b>HIV-1 RNA &lt; 50 copies/mL at week 96, n (%)<sup>a</sup></b>						
n/N (%)	277/379 (73.1)	248/376 (66.0)	282/364 (77.5)	268/364 (73.6)	ND	ND
Difference, % (95% CI)	7.1 (0.5 to 13.7)		3.8 (-2.4 to 10.0)		-	-
<b>Withdrawals<sup>c</sup></b>						
Total, n (%)	91 (23.6)	110 (28.6)	68 (18.5)	88 (24.0)	40 (8.9)	21 (9.4)
<b>SAEs<sup>c</sup></b>						
n (%)	27 (7.0)	33 (8.6)	21 (5.8)	30 (8.2)	22 (4.9)	8 (3.6)
<b>WDAEs<sup>c</sup></b>						
n (%)	6 (1.6)	12 (3.1)	11 (3.0)	24 (6.6)	15 (3.4)	1 (0.4)
<b>Notable harms(s)<sup>c</sup></b>						
	<b>DOR week 0-48</b>	<b>DRV/r week 0-48</b>	<b>DOR/3TC/TDF week 0-48</b>	<b>EFV/FTC/TDF week 0-48</b>	<b>ISG week 0-24</b>	<b>DSG week 0-24</b>
Fasting LDL (mg/dL)						
N (%)	<b>326 (85.1)</b>	<b>318 (83.0)</b>	<b>330 (90.6)</b>	<b>305 (83.8)</b>	<b>371 (83.0)</b>	<b>180 (80.7)</b>
Baseline mean	91.1	91.8	92.0	90.8	112.8	110.2
Mean change (SD)	-4.51 (20.64)	9.92 (27.31)	-1.58 (22.12)	8.74 (25.54)	-18.19 (24.33)	-1.81 (26.36)
Mean difference, 95% CI	-14.61 (-18.15 to -11.06) <sup>d</sup>		-10.01 (-13.53 to -6.49) <sup>d</sup>		-15.29 (-18.99 to -11.59)	
Fasting non-HDL (mg/dL)						
N (%)	<b>329 (85.9)</b>	<b>325 (84.8)</b>	<b>333 (91.5)</b>	<b>314 (86.3)</b>	<b>386 (86.3)</b>	<b>191 (85.6)</b>
Baseline mean	113.3	114.4	115.2	114.8	143.1	139.1
Mean change (SD)	-5.30 (23.28)	13.75 (31.08)	-3.83 (22.59)	13.26 (28.76)	-26.17 (29.84)	-0.55 (29.30)
Mean difference (95% CI)	-19.34 (-23.33 to -15.35) <sup>d</sup>		-17.02 (-20.89 to -13.16) <sup>d</sup>		-23.90 (-28.14 to -19.65)	
<b>Neuropsychiatric AEs</b>						
N	<b>383</b>	<b>383</b>	<b>364</b>	<b>364</b>	<b>447</b>	<b>223</b>
Dizziness	19 (5.0)	15 (3.9)	32 (8.8)	135 (37.1)	10 (2.2)	0 (0.0)
Difference, % (95% CI)	ND		-28.3 (-34.0 to -22.5) <sup>d</sup>		ND	
Sleep disorders and disturbances	-	-	44 (12.1)	93 (25.5)	7 (1.6)	0 (0.0)
Difference, % (95% CI)	ND		-13.5 (-19.1 to -7.9) <sup>d</sup>		ND	
Altered sensorium	-	-	16 (4.4)	30 (8.2)	-	-
Difference, % (95% CI)	ND		-3.8 (-7.6 to -0.3) <sup>d</sup>		ND	

3TC = lamivudine; AE = adverse event; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; DSG = delayed switch group; EFV = efavirenz; FTC = emtricitabine; HDL = high-density lipoprotein cholesterol; ISG = immediate switch group; LDL = low-density lipoprotein; ND = not done; NI = noninferiority; RNA = ribonucleic acid; SAE = serious adverse event; SD = standard deviation; TDF = tenofovir disoproxil fumarate; WDAE = withdrawal due to adverse event.

<sup>a</sup> Snapshot approach under which all missing values were counted as failure.

<sup>b</sup> NI margin 10% (DRIVE-FORWARD and DRIVE-AHEAD) and 8% (DRIVE-SHIFT).

<sup>c</sup> Data through 96 weeks for DRIVE-FORWARD and DRIVE-AHEAD and through 48 weeks for DRIVE-SHIFT.

<sup>d</sup> Statistically significant with adjustment for multiplicity.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> and DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

## Introduction

### Disease Prevalence and Incidence

HIV is responsible for causing a condition that gradually weakens the immune system.<sup>1</sup> HIV is transmitted via body fluids such as blood, semen, genital secretions, and breast milk; most commonly from unprotected sexual intercourse or through sharing contaminated needles and syringes with an infected person.<sup>2</sup> HIV gradually destroys the immune system by selectively destroying CD4 immune cells, which are critical for fighting infections. This compromises the immune system's ability to mount an effective immunological response to opportunistic pathogens over time. HIV infection can progress to AIDS and ultimately death if left untreated. The fatality of HIV has been significantly reduced since the mid-1990s after the invention of highly active forms of antiretroviral (ARV) therapy (ART).<sup>4</sup> Since then, ART has improved steadily with the availability of newer and potent combination therapies. Treatments are aimed at lowering the level of HIV in the body, thereby slowing the spread of the virus and helping the immune system respond to other infections. Patients now have a better opportunity to live a longer, healthier life and decrease their risk of transmitting the virus to others. Newer ARTs have significantly reduced HIV-associated morbidity and mortality and HIV is largely considered a manageable chronic condition.<sup>4</sup> Starting treatment early can increase the probability of living a near-normal lifespan. Patient group input provided to CADTH Common Drug Review (CDR) in relation to this review indicates that stigma is a major concern.

Surveillance data from the Public Health Agency of Canada estimate that, in Canada, a cumulative total of 84,409 cases of HIV had been reported by the end of 2016.<sup>3</sup> The incidence rate in 2016 was 6.4 per 100,000 population, or 2,344 newly reported cases. The number of reported HIV cases is in decline, although there have been periods of fluctuations.<sup>3</sup> The incidence of reported HIV cases declined from 2008 to 2014, but the national diagnosis rate increased by 11.6% in 2016 from the numbers in 2015. Ontario accounted for the highest number and proportion of reported HIV cases in 2016 (37.6%), followed by Quebec (25.3%) and Alberta (12.0%).<sup>3</sup> The provincial and territorial HIV diagnosis rates varied notably across the country, with the highest diagnosis rates found in Saskatchewan (7.4%, 15.1 per 100,000), Manitoba (5.4%, 9.5 per 100,000), Quebec (7.1 per 100,000) and Alberta (6.6 per 100,000).<sup>3</sup> Age distribution showed that the highest incidence of HIV cases was in people 30 to 39 years old (28.7%) and among males (76.7%). Among adults with known exposure (61.6% of all cases), the most common exposure categories were "men who have sex with men" (44.1%), followed by heterosexual contact (32.3%), and injection drug use (15.1%). Race/ethnicity distribution showed that the following races accounted for the most commonly reported HIV cases: white (40.4%), black (21.9%), and Indigenous (21.2%).<sup>3</sup>

### Standards of Therapy

The clinical expert consulted for this review indicated that the US Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*<sup>4</sup> inform clinical practice in Canada. According to the recommendations, ARV regimens for treatment-naïve patients generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three classes: an integrase strand transfer inhibitor (InSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a



pharmacokinetic enhancer (booster) (cobicistat or ritonavir).<sup>4</sup> The following regimens are recommended by the DHHS panel for initial treatment among newly diagnosed patients: bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC), dolutegravir/abacavir/lamivudine (DTG/ABC/3TC — only for patients who are HLA-B\*5701 negative), dolutegravir/tenofovir disoproxil fumarate/emtricitabine (DTG/TDF)/FTC), and raltegravir/TDF/FTC; with 3TC as an alternative to FTC and TDF used in consideration of bone and renal toxicities and lipid levels.<sup>4</sup> Notably, doravirine/TDF/3TC (DOR/TDF/3TC) and DOR plus TAF/FTC are recommended as initial regimens in certain clinical situations, including patients at high cardiac risk and hyperlipidemia.<sup>4</sup>

Once initiated, ARTs should be continued with the following key treatment goals: maximally and durably suppress plasma HIV ribonucleic acid (RNA) below detectable limits (< 50 copies/mL); restore and preserve immunologic function (increase CD4 cell count); reduce HIV-associated morbidity; prolong the duration and quality of survival; and prevent HIV transmission. Current ARTs are not curative; they require lifelong administration and therefore high levels of adherence to achieve treatment goals.<sup>4</sup> To simplify ARV regimens and support long-term adherence, several single-table regimens (STRs) are available, alongside non-STRs, providing clinicians and patients with an array of therapeutic options.

For treatment-experienced patients with viral suppression, the DHHS guidelines do not provide a list of recommended therapies; the selection of a new ARV regimen should be based instead on patients' previous ART histories, including virologic responses, past ART-associated toxicities and intolerances, resistance-test results, drug-drug interactions, and pill burden, in addition to other non-clinical considerations. For switching to a two-drug regimen, the DHHS guidelines include two regimen options with strong supporting evidence: a boosted PI plus FTC or 3TC, or DTG plus rilpivirine. Switching to a monotherapy regimen is not recommended due to a lack of efficacy and development of treatment resistance.<sup>4</sup>

According to the clinical expert, there is no pressing therapeutic need that is unmet by current ARV therapies. However, new regimens (preferably STRs) that are effective, safe, and tolerable would be welcome.

## Drug

DOR (Pifeltro, 100 mg) is an oral tablet indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to doravirine. The Health Canada recommended dose is one 100 mg tablet taken orally once daily with or without food. Reimbursement is being sought by the manufacturer in accordance with the indication.

DOR is an NNRTI of HIV-1. NNRTIs act by binding to and blocking HIV reverse transcriptase (an enzyme essential to the HIV replication cycle), thereby preventing HIV from replicating.<sup>10</sup>

The objective of this systematic review was to evaluate the beneficial and harmful effects of DOR, in combination with other ARV medicinal products, for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to DOR.

A table describing key characteristics of STRs and other commonly recommended ARV regimens is presented in Table 2.

**Table 2: Key Characteristics of Commonly Recommended Antiretroviral Therapy Regimens<sup>a</sup>**

Comparator regimens	Brand	Dosage strengths	Indications <sup>b</sup>	Key Side Effects/Safety Issues
<b>Single-tablet regimens</b>				
BIC/TAF/FTC	Biktarvy	<b>BIC:</b> 50 mg <b>FTC:</b> 200 mg <b>TAF:</b> 25 mg	A complete regimen for the treatment of HIV-1 infection in adults with no known substitution associated with resistance to the individual components of Biktarvy <sup>11</sup>	<b>BIC:</b> diarrhea, nausea, headache, fatigue, abnormal dreams, dizziness, and insomnia <sup>11</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup> <b>TAF:</b> similar to TDF, but may have less renal and bone toxicity <sup>14</sup>
DTG/ABC/3TC	Triumeq	<b>DTG:</b> 50 mg <b>ABC:</b> 600 mg <b>3TC:</b> 300 mg	Treatment of HIV-1 infection in adults and adolescents aged $\geq 12$ years and weighing $\geq 40$ kg <sup>15</sup>	<b>DTG:</b> insomnia, headache, depression; early benign increase in SCr <sup>12,13</sup> <b>ABC:</b> risk of severe hypersensitivity reaction in genetically susceptible patients; possible increased risk for MI <sup>12,13</sup> <b>3TC:</b> generally well tolerated <sup>12</sup>
EVG/c/TAF/FTC	Genvoya <sup>c</sup>	<b>EVG:</b> 150 mg <b>c:</b> 150 mg <b>FTC:</b> 200 mg <b>TAF:</b> 10 mg	A complete regimen for the treatment of HIV-1 infection in adults and pediatric patients aged $\geq 12$ years (and weighing $\geq 35$ kg) and with no known RAMs to the individual components of Genvoya <sup>16</sup>	<b>EVG:</b> nausea, diarrhea, insomnia, headache, depression; early benign increase in SCr <sup>12,13</sup> <b>c:</b> can falsely increase SCr <sup>13</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup> <b>TAF:</b> similar to TDF, but may have less renal and bone toxicity <sup>14</sup>
RPV/TAF/FTC	Odefsey <sup>c</sup>	<b>RPV:</b> 25 mg <b>TAF:</b> 25 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 $\leq 100,000$ copies/mL <sup>17</sup>	<b>RPV:</b> depression, insomnia, rash, headache; early benign increase in SCr <sup>12</sup> <b>TAF:</b> similar to TDF, but may have less renal and bone toxicity <sup>14</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup>
DTG/RPV	Juluca	<b>DTG:</b> 50 mg <b>RPV:</b> 25 mg	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) <sup>18</sup>	<b>DTG:</b> insomnia, headache, depression; early benign increase in SCr <sup>12,13</sup> <b>RPV:</b> depression, insomnia, rash, headache; early benign increase in SCr <sup>12</sup>
DRV/c/TDF/FTC	Symtuza	<b>DRV:</b> 800 mg <b>c:</b> 150 mg <b>TAF:</b> 10 mg <b>FTC:</b> 200 mg	Indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight of at least 40 kg) and with no known mutations associated with resistance to the individual components of Symtuza <sup>19</sup>	<b>DRV:</b> diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation) <sup>12,13</sup> <b>c:</b> can falsely increase SCr <sup>13</sup> <b>TAF:</b> similar to TDF, but may have less renal and bone toxicity <sup>14</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup>
EVG/c/TDF/FTC	Stribild <sup>c</sup>	<b>EVG:</b> 150 mg <b>c:</b> 150 mg	A complete regimen for the treatment of adults aged $\geq 18$	<b>EVG:</b> nausea, diarrhea, insomnia, headache, depression; early benign

Comparator regimens	Brand	Dosage strengths	Indications <sup>b</sup>	Key Side Effects/Safety Issues
		<b>FTC:</b> 200 mg <b>TDF:</b> 300 mg	years infected with HIV-1 with no known mutations to the InSTI class, tenofovir, or FTC <sup>20</sup>	increase in SCr <sup>12,13</sup> <b>c:</b> can falsely increase SCr <sup>13</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>12</sup>
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>21</sup>	<b>RPV:</b> depression, insomnia, rash, headache; early benign increase in SCr <sup>12</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>12</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</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 agents for the treatment of HIV-1 infection in adults <sup>22</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>12,13</sup> <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>12</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup>
<b>Additional relevant comparator regimens</b>				
DRV/c + TAF/FTC	Prezcobix <sup>c</sup>  Descovy	<b>DRV/c:</b> 800 mg/150 mg  <b>TAF/FTC:</b> 10 mg/200 mg 25 mg/200 mg	In combination with other ARV agents for the treatment of HIV infection in treatment-naïve and in treatment-experienced patients without DRV RAMs <sup>23</sup>  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>24</sup>	<b>DRV:</b> diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation) <sup>12,13</sup> <b>c:</b> can falsely increase SCr <sup>13</sup> <b>TAF:</b> similar to TDF, but may have less renal and bone toxicity <sup>14</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup>
DTG + TAF/FTC	Tivicay  Descovy	<b>DTG:</b> 50 mg  <b>TAF/FTC:</b> 10 mg/200 mg 25 mg/200 mg	Treatment of HIV-1 infection in adults and in InSTI-naïve children weighing ≥ 30 kg <sup>25</sup>  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>24</sup>	<b>DTG:</b> insomnia, headache, depression; early benign increase in SCr <sup>12,13</sup> <b>TAF:</b> similar to TDF, but may have less renal and bone toxicity <sup>14</sup> <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup>
DRV+ r + TDF/FTC	Prezista <sup>c</sup>  Norvir <sup>c</sup>	<b>DRV:</b> 800 mg  <b>r:</b> 100 mg	Co-administered with 100 mg ritonavir and with other ARV agents for the treatment of HIV-1 infection <sup>26</sup>  In combination with other ARV	<b>DRV:</b> diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval

Comparator regimens	Brand	Dosage strengths	Indications <sup>b</sup>	Key Side Effects/Safety Issues
	Truvada, generics	<b>TDF:</b> 300 mg <b>FTC:</b> 200 mg	agents for the treatment of HIV infection when therapy is warranted <sup>27</sup>  In combination with other ARV agents (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults <sup>28</sup>	prolongation) <sup>12,13</sup>  <b>r:</b> diarrhea, nausea, headache, paresthesias, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation) <sup>12,13</sup>  <b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>13</sup>  <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup>
DTG + TDF/FTC	Tivicay	<b>DTG:</b> 50 mg	Treatment of HIV-1 infection in adults and in InSTI-naïve children weighing ≥ 30 kg <sup>25</sup>	<b>DTG:</b> insomnia, headache, depression; early benign increase in SCr <sup>12,13</sup>
	Truvada, generics	<b>TDF:</b> 300 mg <b>FTC:</b> 200 mg	In combination with other ARV agents (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults <sup>28</sup>	<b>TDF:</b> renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity <sup>12</sup>  <b>FTC:</b> discoloration of skin (hands/feet) <sup>13</sup>

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; 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>

Sources: Biktarvy product monograph,<sup>11</sup> Prezcoibix product monograph,<sup>23</sup> Tivicay product monograph,<sup>25</sup> Descovy product monograph,<sup>24</sup> Genvoya product monograph,<sup>16</sup> Odefsey product monograph,<sup>17</sup> Triumeq product monograph,<sup>15</sup> Truvada product monograph,<sup>28</sup> Prezista product monograph,<sup>26</sup> Norvir product monograph,<sup>27</sup> Stribild product monograph,<sup>20</sup> Complera product monograph,<sup>21</sup> Atripla product monograph,<sup>22</sup> Juluca product monograph,<sup>18</sup> Symtuza product monograph,<sup>19</sup> e-CPS,<sup>12</sup> RxFiles,<sup>13</sup> AIDSinfo.<sup>1</sup>

## Objectives and Methods

### Objectives

To perform a systematic review of the beneficial and harmful effects of DOR 100 mg in combination with other ARV medicinal products for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine.

### Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review in addition to those meeting the selection criteria presented in Table 3.

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

<b>Patient Population</b>	Adults with HIV-1 without past or present evidence of viral resistance to doravirine  Subgroups: <ul style="list-style-type: none"> <li>• Patients who are naive to, switched, or failed treatment</li> <li>• Baseline viral load (in treatment-naive population)</li> </ul>
<b>Intervention</b>	Doravirine 100 mg tablet taken orally once daily in combination with other antiretrovirals
<b>Comparators</b>	Standard care dual- or triple-ARV complete regimen
<b>Outcomes</b>	<p><b>Efficacy outcomes:</b></p> <ul style="list-style-type: none"> <li>• Proportion of patients with VL &lt; 50 copies / mL (FDA-defined snapshot algorithm)<sup>a</sup></li> <li>• Proportion of patients with VL ≥ 50 copies / mL (FDA-defined snapshot algorithm)<sup>a</sup></li> <li>• CD4 cell count</li> <li>• Development of drug resistance<sup>a</sup></li> <li>• Quality of life<sup>a</sup></li> <li>• Adherence to ARV therapy<sup>a</sup></li> </ul> <p><b>Harms outcomes:</b></p> <ul style="list-style-type: none"> <li>• SAEs</li> <li>• AEs</li> <li>• WDAEs</li> <li>• Notable harms: bone-related AEs, renal toxicity, lipid profile, cardiovascular disease or events, neuropsychiatric events (including dizziness, sleep disorders and disturbances, and altered sensorium), altered hepatic enzymes, skin disorders</li> </ul>
<b>Study Design</b>	Published and unpublished phase III and IV RCTs

ARV = antiretroviral; AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse event; VL = viral load; WDAE = withdrawal due to adverse event.

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

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 All (1946–) via Ovid; Embase (1974–) via 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 concept was Pifeltro (doravirine).

No methodological filters were applied to limit retrieval by study type. 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 December 12, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on April 10, 2019. 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, clinical trial registries, and databases. 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.

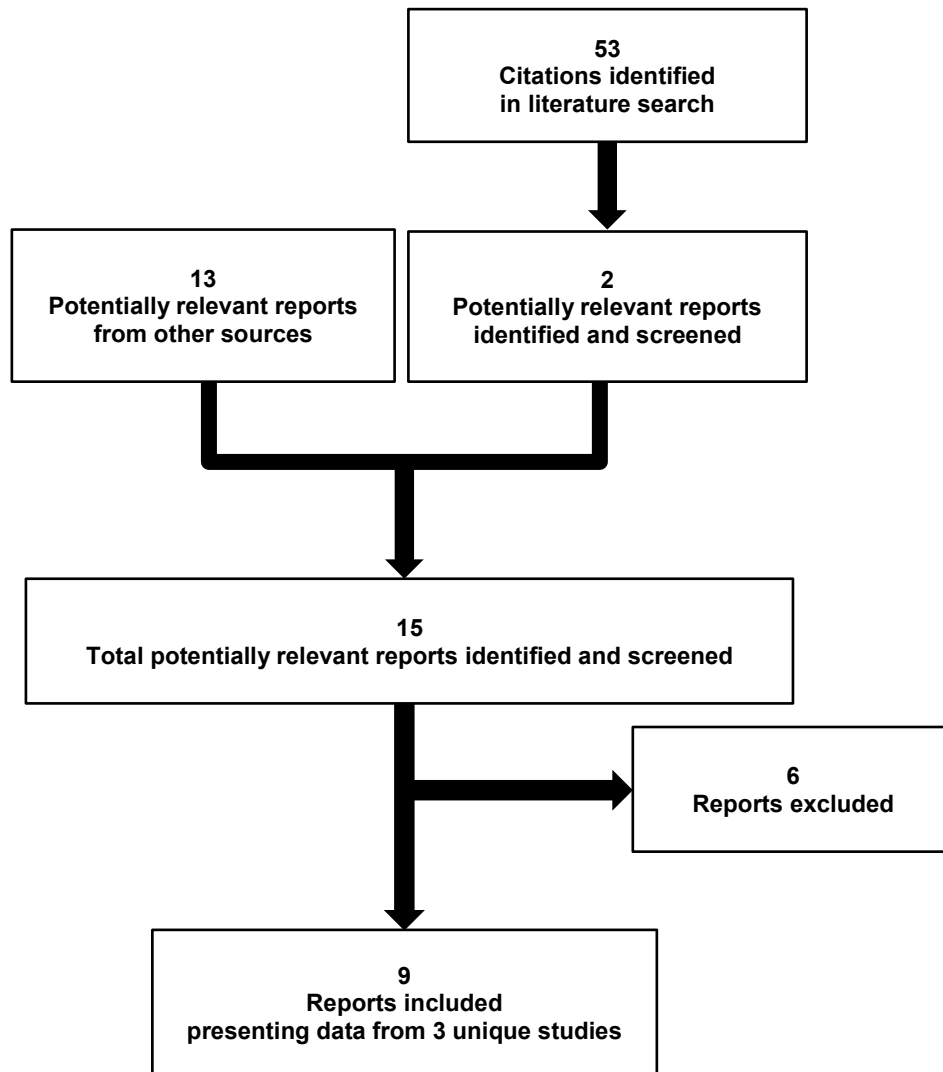
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final 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 4.

## Results

### Findings from the Literature

Three 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**

	DRIVE-FORWARD	DRIVE-AHEAD	DRIVE-SHIFT	
<b>DESIGNS &amp; POPULATIONS</b>	<b>Study design</b>	DB, MC, AC RCT	DB, MC, AC RCT	OL, MC, AC RCT
	<b>Locations</b>	Australia, Canada, Central and Western Europe, Chile, Argentina, Russia, South Africa, US, and Puerto Rico	Australia and New Zealand, Canada, Central and South America, Western Europe, Israel, Russia, South Africa, Taiwan, Thailand, US, and Puerto Rico	Australia and New Zealand, Canada, Central and South America, Central and Western Europe, Israel, Russia, South Korea, US, and Puerto Rico
	<b>Randomized (N)</b>	769	734	673
	<b>Inclusion criteria</b>	Naive to ART		Patients on a stable antiretroviral regimen, who were virologically suppressed for ≥ 6 months on pre-specified regimens No or stable dose of lipid-lowering therapy
		<ul style="list-style-type: none"> <li>• ≥ 18 years (confirmed HIV-1–positive) with ≥ 1,000 copies/mL (DRIVE-FORWARD and DRIVE-AHEAD) or &lt; 40 copies/mL (DRIVE-SHIFT) plasma HIV-1 RNA<sub>b</sub> at screening</li> <li>• ALP ≤ 3.0 x ULN, AST and ALT ≤ 5.0 x ULN</li> <li>• Creatinine clearance ≥ 50 mL/min</li> <li>• Clinically stable with no signs or symptoms of active infection</li> <li>• Unlikely to become pregnant or to impregnate a partner</li> <li>• Patients who completed week 96 visit (DRIVE-FORWARD and DRIVE-AHEAD) or week 48/144 visit (DRIVE-SHIFT) and deemed clinically appropriate candidates were eligible to enter the extension study</li> </ul>		
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Previous or current condition, therapy, laboratory abnormality, or other circumstance that might interfere with study results or patients’ participation for the full duration of the study</li> <li>• Use of recreational or illicit drugs, recent history of drug or alcohol abuse or dependence</li> <li>• Treated for hepatitis B or other viral infection with an agent that is co-active against HIV-1</li> <li>• No prior history of virologic failure on any regimen or resistance to study drugs</li> <li>• Recent use or future need of systemic immunosuppressive therapy or immune modulators</li> <li>• Significant hypersensitivity or other contraindication</li> <li>• Current (active) diagnosis of acute hepatitis</li> </ul>			
<b>DRUGS</b>	<b>Intervention</b>	DOR 100 mg in combination with FTC/TDF 200 mg/300 mg or ABC/3TC 600 mg/300 mg q.d. orally	DOR/3TC/TDF 100 mg/300 mg/300 mg	<i>Immediate switch group:</i> DOR/3TC/TDF 100 mg/300 mg/300 mg orally q.d. from study week 1
	<b>Comparator(s)</b>	DRV 800 mg with RTV 100 mg in combination with FTC/TDF 200 mg/300 mg or ABC/3TC 600 mg/300 mg q.d. orally	EFV/FTC/TDF 600 mg/200 mg/300 mg q.d. orally	<i>Delayed switch group:</i> Week 1 and 24: Ritonavir- or cobicistat-boosted PI, or cobicistat-boosted EVG (InSTI), or an NNRTI, each with 2 NRTIs orally week 24 onwards: DOR/3TC/TDF 100 mg/300 mg/300 mg q.d. orally



		DRIVE-FORWARD	DRIVE-AHEAD	DRIVE-SHIFT
DURATION	Randomized <sup>c</sup>	96 weeks	96 weeks	48 weeks
	Follow-up	14 days	14 days	14 days
	Extension (OL)	96 weeks	96 weeks	144 weeks
OUTCOMES	<b>Primary end point</b>	Proportion of patients achieving plasma HIV-1 RNA level < 50 copies/mL at week 48	Proportion of patients achieving plasma HIV-1 RNA level < 50 copies/mL at week 48 Proportion of patients with neuropsychiatric AEs	Proportion of patients maintaining HIV-1 RNA < 50 copies/mL at week 48 in the ISG and at week 24 in the DSG
	<b>Other end points</b>	<i>Secondary efficacy:</i> Proportion of patients achieving plasma HIV-1 RNA level < 50 copies/mL at week 96 CD4+ T-cell count at week 48 and 96  <i>Exploratory efficacy:</i> Viral drug resistance	<i>Secondary efficacy:</i> Proportion of patients achieving plasma HIV-1 RNA level < 50 copies/mL at week 48 and 96 CD4+ T-cell count at week 48 and week 48 and 96  <i>Exploratory efficacy:</i> Viral drug resistance	<i>Secondary efficacy:</i> Proportion of patients maintaining HIV-1 RNA < 50 copies/mL at weeks 24 and 48 in each treatment group  Proportion of patients with HIV-1 RNA ≥ 50 copies/mL at weeks 24 and 48 in each treatment group CD4+ T-cell count at week 24 and 48  <i>Exploratory efficacy:</i> Viral drug resistance HRQoL measures: EQ-5D-5L
		<i>Safety outcomes:</i> Monitoring and recording of lipid profile and all AEs and SAEs (e.g., laboratory, clinical)		
NOTES	<b>Publications</b>	Molina et al. (2018) <sup>29</sup>	Orkin et al. (2018) <sup>30</sup>	None

3TC = lamivudine; ABC = abacavir; AC = active-controlled; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; ART = antiretroviral therapy; DB = double-blind; DOR = doravirine; DRV = darunavir; DSG = delayed switch group; EFV = efavirenz; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EVG = elvitegravir; FTC = emtricitabine; HRQoL = health-related quality of life; InSTI = integrase strand transfer inhibitor; ISG = immediate switch group; MC = multi-centre; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OL; PI = protease inhibitor; q.d. = daily; RNA = ribonucleic acid; RTV = ritonavir; SAE = serious adverse event; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal.

Note: Seven additional reports were included: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report,<sup>9</sup> the FDA report for Pifeltro<sup>31</sup>, and the Health Canada Reviewers' Report.<sup>32</sup>

<sup>a</sup> As determined by a positive result on an enzyme-immuno assay.

<sup>b</sup> Determined by the central laboratory.

<sup>c</sup> Comprising the base study, double-blind for DRIVE-FORWARD and DRIVE-AHEAD, open-label for DRIVE-SHIFT.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

## Included Studies

### Description of Studies

Three trials met the inclusion criteria for this review (Table 3). Study-specific details are listed in Table 4, and schematics of the trial designs are included in Figure 2, 3, and 4 in Appendix 4.

### *Treatment-Naive*

DRIVE-FORWARD (P-018, N = 769)<sup>5,6</sup> and DRIVE-AHEAD (P-021, N = 728)<sup>7,8</sup> were similarly designed phase III, randomized (1:1), multi-centre, double-blind (DB), double-dummy, parallel-group, active-controlled, noninferiority trials; and included ART-naive patients with plasma HIV-1 RNA  $\geq$  1,000 copies/mL at screening. In DRIVE-FORWARD, the efficacy and safety of DOR (100 mg) once daily was compared with DRV/r (800 mg/100 mg) once daily, each given in combination with investigator-selected FTC/TDF 200 mg/300 mg, supplied as Truvada once daily, or ABC/3TC 600 mg/300 mg, supplied as Epzicom or Kivexa once daily. DRIVE-AHEAD was designed to evaluate the comparative safety and efficacy of DOR/3TC/TDF 100 mg/300 mg/TDF 300 mg once daily compared with efavirenz/FTC/TDF 600 mg/200 mg/300 mg (EFV/FTC/TDF, supplied as Atripla) once daily. The primary efficacy end point in both trials was the proportions of patients with HIV-1 RNA  $<$  50 copies/mL assessed at week 48. The following secondary efficacy outcomes were also measured through week 96: the proportions of patients with HIV-1 RNA  $<$  and  $\geq$  50 copies/mL, and change from baseline in CD4 cell count. Notable safety end points included lipid profile and neuropsychiatric adverse events (AEs) including but not limited to dizziness, sleep disorders, and altered sensorium (e.g., depressed level of consciousness, lethargy, somnolence, or syncope).

In both trials, patients who met the entry criteria underwent randomization, which was conducted centrally using an interactive voice/Web response system (IVRS/IVWS) in a 1:1 ratio. Patients in DRIVE-FORWARD were stratified by HIV-1 RNA level at screening ( $\leq$  or  $>$  100,000 copies/mL) and NRTI background therapy (FTC/TDF or ABC/3TC, as selected by the investigator); and patients in DRIVE-AHEAD were stratified by screening HIV-1 RNA ( $\leq$  or  $>$  100,000 copies/mL) and hepatitis B and/or C co-infection status.

Both DRIVE-FORWARD and DRIVE-AHEAD had a total DB duration of 96 weeks (the base study), in which the first 48 weeks were used for the primary analyses. All eligible patients who provided consent to continue their treatment entered the open-label (OL) study extension, receiving DOR/3TC/TDF once daily or DOR once daily in combination with NRTI background therapy for an additional 96 weeks. Due to the minimal data available for the extension period, this review will be limited to the duration of the base study. Patients who met the criteria for protocol-defined virologic failure (PDVF) at any point during the study discontinued from the trial, regardless of the reason. The criteria for PDVF included having a confirmed (i.e., two consecutive measures at least one week apart) HIV-1 RNA  $\geq$  200 copies/mL at week 24 or week 36, confirmed HIV-1 RNA  $\geq$  50 copies/mL at week 48 (termed non-responders), or confirmed HIV-1 RNA  $\geq$  50 copies/mL after an initial response of HIV-1 RNA  $<$  50 copies/mL at any time during the study (termed rebounders).

### *Treatment-Switch*

DRIVE-SHIFT (P-024, N = 673)<sup>9</sup> was a phase III, randomized (1:1), multi-centre, OL, parallel-group, active-controlled, noninferiority trial that included virologically suppressed patients (defined as HIV-1 RNA  $<$  40 copies/mL) on a stable ARV regimen. This study evaluated a switch from a stable ARV regimen of a ritonavir- or cobicistat-boosted PI, or cobicistat-boosted integrase strand transfer inhibitor (InSTI), or NNRTI, each administered with two NRTIs, to DOR/3TC/TDF. Following a screening visit to determine the entry criteria, eligible patients were randomized in a 2:1 ratio to the immediate switch group (ISG) to receive DOR/3TC/TDF on study day 1 or to the delayed switch group (DSG) to start DOR/3TC/TDF at week 24. Patients in the DSG arm received their baseline regimens

(described above) until week 24. Randomization was conducted centrally using an IVRS/IVWS; an allocation schedule was computer-generated.

The efficacy and safety outcomes were similar to the trials described above, and included the proportions of patients with HIV RNA < 50 copies/mL at week 48 (primary outcome), HIV RNA  $\geq$  50 copies/mL, CD4 cell count, lipid profile, and neuropsychiatric AEs at week 24 and 48. Due to the differences in DOR/3TC/TDF exposure between the treatment arms, the outcomes were compared between the ISG arm at week 48 and the baseline regimen at week 24 for the DSG arm (primary time point) as well as between the ISG arm at week 24 and baseline regimen at week 24 for the DSG arm (secondary time point).

The trial consisted of a 48-week base study, used for the primary analyses (described in Table 4). Patients who completed the base study and were eligible could enter into the OL study extension, receiving DOR/3TC/TDF once daily for up to 192 weeks total. Due to the minimal data available for the extension period, this review is limited to the duration of the base study. Patients who met the criteria for PDVF at any point during the study discontinued from the trial, regardless of the reason.

This CDR review will be limited to the base study period for each trial.

## Populations

### *Inclusion and Exclusion Criteria*

#### **Treatment-Naive**

The inclusion and exclusion criteria of DRIVE-FORWARD and DRIVE-AHEAD were similar and are described in Table 4. Both trials enrolled ART-naive, HIV-positive patients aged  $\geq$  18 years with screening for HIV-1 RNA levels  $\geq$  1,000 copies/mL, and without any exclusionary laboratory values (alkaline phosphatase  $>$  3.0 x upper limit of normal [ULN], alanine transaminase and aspartate transaminase  $>$  5.0 x ULN each, creatinine clearance  $<$  50 mL/min) and any signs or symptoms of active infection. Patients with current use of recreational or illicit drugs or a recent history of drug or alcohol abuse or dependence as well as those with decompensated liver disease, liver cirrhosis, and a Child–Pugh class C score or Pugh–Turcotte score above 9 were excluded from the trials. In addition, patients were excluded if they had a documented or known history of resistance to any of the study drugs; were previously treated for a viral infection, e.g., hepatitis B with an agent that is active against HIV-1; recently used systemic immunosuppressive therapy or immune modulators; had a history or current evidence of any condition, therapy, laboratory abnormality or other circumstances that might confound the results of the study or potentially interfere with study compliance; and had a current (active) diagnosis of acute hepatitis. Notably, patients with chronic hepatitis B and C were allowed to enter the study as long as they fulfilled all entry criteria, had stable liver function tests, and had no significant impairment of hepatic synthetic function (defined as a serum albumin  $<$  2.8 mg/dL or an international normalized ratio  $>$  1.7).

#### **Treatment-Switch**

Patients in the DRIVE-SHIFT trial were HIV-1–positive adults ( $\geq$  18 years) with an undetectable level of HIV-1 RNA ( $<$  40 copies/mL) on a stable (six months or longer) ARV regimen consisting of a ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir) or cobicistat-boosted EVG or an NNRTI (specifically, EFV, nevirapine, or rilpivirine) with a backbone of two NRTIs, and had no history of prior virologic failure.

Additional major inclusion criteria included no previous history of receiving any experimental NNRTIs, no or stable lipid-lowering therapy, no exclusionary laboratory values at screening (based on criteria as above), and a clinically stable condition without any signs or symptoms of active infection.

Exclusion criteria for DRIVE-SHIFT were similar to those of the DRIVE-FORWARD and DRIVE-AHEAD trials, and included current use of recreational or illicit drugs or a recent history of drug or alcohol abuse or dependence; patients with decompensated liver disease, liver cirrhosis and a Child–Pugh class C score or Pugh–Turcotte score above 9; resistance to any of the study drugs; previous treatment for a viral infection with an agent that is active against HIV-1; recent use of systemic immunosuppressive therapy or immune modulators; history or current evidence of any condition, therapy, laboratory abnormality or other circumstances that might confound the results of the study or potentially interfere with study compliance; and current (active) diagnosis of acute hepatitis.

**Baseline Characteristics**

Baseline characteristics were generally similar between groups within trials (Table 5). The majority of the patients were male (> 80%). Patients who were treatment-naïve were younger, with a mean age between 32 and 36 years, whereas patients who were treatment-experienced had a mean age of 43 years. Baseline CD4 cell counts were higher among treatment-experienced patients as they were on viral suppressive therapies at baseline. Approximately 20% of treatment-naïve patients had a baseline plasma HIV-1 RNA level of > 100,000 copies/mL. The frequency of patients with AIDS ranged from 10% to 15% among treatment-naïve patients, and approximately 15% to 18% among treatment-experienced patients.

Medical histories between-treatment groups within trials were largely similar; with the exception of gastrointestinal disorders occurring at a greater frequency in the DRV/r arm of DRIVE-FORWARD and psychiatric and immune system disorders occurring at a greater frequency in the ISG arm of DRIVE-SHIFT. The baseline regimens between-treatment groups in DRIVE-SHIFT were similar, and the majority of the patients received a ritonavir-boosted PI (~ 70%) and NNRTIs (~ 24%). A small but similar proportion of patients in each arm within the trials received lipid-lowering therapy.

**Table 5: Summary of Baseline Characteristics**

	DRIVE-FORWARD		DRIVE-AHEAD		DRIVE-SHIFT	
	DOR (N = 383)	DRV/r (N = 383)	DOR/3TC/TDF (N = 364)	EFV/FTC/TDF (N = 364)	ISG (N = 447)	DSG (N = 223)
<b>Demographic and clinical characteristics</b>						
Male, n (%)	319 (83.3)	326 (85.1)	305 (83.8)	311 (85.4)	372 (83.2)	194 (87.0)
Race n (%)						
White	280 (73.1)	280 (73.1)	177 (48.6)	170 (46.7)	344 (77.0)	168 (75.3)
Black	86 (22.5)	88 (23.0)	67 (18.4)	68 (18.7)	56 (12.5)	34 (15.2)
Asian	7 (1.8)	7 (1.8)	59 (16.2)	65 (17.9)	17 (3.8)	8 (3.6)
Age (years)						
Mean (SD)	34.8 (10.5)	35.7 (10.7)	33.6 (10.5)	32.7 (9.9)	43.1 (10.1)	43.7 (10.6)
Baseline CD4 cell count (cells/mm <sup>3</sup> )	432.6 (208.4)	411.9 (229.6)	434.9 (217.9)	415.5 (210.6)	664.9 (295.3)	649.9 (279.2)
Mean (SD)						

	DRIVE-FORWARD		DRIVE-AHEAD		DRIVE-SHIFT	
	DOR (N = 383)	DRV/r (N = 383)	DOR/3TC/TDF (N = 364)	EFV/FTC/TDF (N = 364)	ISG (N = 447)	DSG (N = 223)
Baseline plasma HIV-1 RNA (log <sub>10</sub> copies/mL) Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.4 (0.7)	4.5 (0.7)	NR	NR
Baseline plasma HIV-1 RNA, n (%) ≤ 100,000 copies/mL < 50 copies/mL	300 (78.3) -	308 (80.4) -	291 (79.9) -	282 (77.5) -	- 436 (97.5)	- 222 (99.6)
History of AIDS, n (%) Yes	36 (9.4)	37 (9.7)	46 (12.6)	53 (14.6)	80 (17.9)	35 (15.7)
Baseline hepatitis status HBV and/or HCV positive	11 (2.9)	18 (4.7)	11 (3.0)	9 (2.5)	14 (3.1)	9 (4.0)
HBV positive only	4 (1.0)	12 (3.1)	9 (2.5)	8 (2.2)	12 (2.7)	7 (3.1)
HCV positive only	7 (1.8)	6 (1.6)	2 (0.5)	1 (0.3)	2 (0.4)	2 (0.9)
HBV and HCV negative	372 (97.1)	365 (95.3)	353 (97.0)	355 (97.5)	433 (96.9)	214 (96.0)
<b>Medical history (≥ 5% difference in incidence between-treatment arms)</b>						
Gastrointestinal disorders	84 (21.9)	112 (29.2)	-	-	-	-
Immune system disorders	-	-	-	-	95 (21.3)	29 (13.0)
Drug hypersensitivity	-	-	-	-	46 (10.3)	13 (5.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	-	-	-	-	85 (19.0)	31 (13.9)
Psychiatric disorders	-	-	-	-	157 (35.1)	59 (26.5)
<b>ART history, n (%)</b>	NA	NA	NA	NA		
Ritonavir-boosted PI	NA	NA	NA	NA	312 (69.8)	155 (69.5)
ATV					96 (21.5)	43 (19.3)
DRV					161 (36.0)	81 (36.3)
LPV					54 (12.1)	31 (13.9)
Cobicistat-boosted PI	NA	NA	NA	NA	5 (1.1)	1 (0.4)
DRV						
Cobicistat-boosted elvitegravir					25 (5.6)	12 (5.4)
NNRTI					106 (23.7)	55 (24.7)
EFV					78 (17.4)	36 (16.1)
NVP					17 (3.8)	12 (5.4)
RPV					11 (2.5)	7 (3.1)
Duration of ART regimen Prior to enrolment (months), mean (SD)	NA	NA	NA	NA	56.6 (38.4)	58.6 (37.0)
Lipid-lowering therapy	10 (2.6)	11 (2.9)	12 (3.3)	14 (3.8)	31 (6.9)	12 (5.4)
<b>Co-administered or prior backbone NRTIs, n (%)</b>						
TDF/FTC	316 (82.5)	312 (81.5)	-	364 (100)	330 (73.8)	154 (69.1)
TAF/FTC	-	-	-	-	22 (4.9)	11 (4.9)
ABC/3TC	48 (12.5)	43 (11.2)	-	-	61 (13.6)	28 (12.6)
ZDV/3TC	-	-	-	-	23 (5.1)	19 (8.5)

	DRIVE-FORWARD		DRIVE-AHEAD		DRIVE-SHIFT	
	DOR (N = 383)	DRV/r (N = 383)	DOR/3TC/TDF (N = 364)	EFV/FTC/TDF (N = 364)	ISG (N = 447)	DSG (N = 223)
TDF/3TC	-	-	364 (100)	-	10 (2.2)	10 (4.5)
Others	-	-	-	-	1 (0.2)	1 (0.4)

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV = atazanavir; DOR = doravirine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; DSG = delayed switch group; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; HCV = hepatitis C virus; ISG = immediate switch group; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; SD = standard deviation; RNA = ribonucleic acid; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

## Interventions

### *Treatment-Naive*

Both trials used a double-dummy design to maintain blinding, with matching placebo for active treatments. Patients in DRIVE-FORWARD were randomized (1:1) to receive DOR 100 mg or DRV/r (800 mg/100 mg), each given in combination with fixed-dose combination (FDC) FTC/TDF (200 mg/300 mg) or ABC/3TC (600 mg/300 mg), administered orally and once daily. DOR and ABC/3TC were taken without regard to food; whereas DRV/r and FTC/TDF were taken with food. Patients with hepatitis B were selectively given FTC/TDF.

Patients in DRIVE-AHEAD received oral once-daily dosages of either DOR/3TC/TDF (100 mg/300 mg/300 mg, plus placebo for EFV/FTC/TDF) or EFV/FTC/TDF (600 mg/200 mg/300 mg, plus placebo for DOR/3TC/TDF) FDC, as determined by patients' 1:1 random assignment. DOR/3TC/TDF was taken at approximately the same time of the day without regard to food, whereas EFV/FTC/TDF was taken at bedtime on an empty stomach.

### *Treatment-Switch*

Patients in DRIVE-SHIFT were randomized (2:1) to receive oral once-daily dosages of DOR/3TC/TDF immediately on day 1 in the ISG arm or continued their baseline regimen (ritonavir- or cobicistat-boosted PI, e.g., atazanavir, darunavir [DRV], or lopinavir, or cobicistat-boosted InSTI (e.g., EVG, or an NNRTI, e.g., EFV, NVP, or rilpivirine; each administered with two NRTIs) until they switched to DOR/3TC/TDF at week 24 in the DSG arm, administered at approximately the same time of the day without regard to food.

No rescue or supportive medications or dose modification of the study medication was allowed during the treatment period of any trial; with the exception of a recommended dosing interval adjustment of FTC/TDF in DRIVE-FORWARD to one tablet every 48 hours in patients with creatinine clearance of 30 mL/min to 49 mL/min. Unless specifically prohibited, all trials allowed patients to receive concomitant medications for their clinical conditions barring potential drug-drug interaction, e.g., oral or other hormonal contraception and new HCV treatments. Patients in DRIVE-SHIFT were allowed to initiate or modify lipid-lowering therapy. Notable prohibited medications included immune-therapy agents or other immunosuppressive therapy (except for short courses of corticosteroids, specialized treatment for Kaposi's sarcoma, malignancy, and hepatitis), moderate or potent inducers of CYP3A, and medications that may interact with any of the study drugs.

## Outcomes

### *Treatment-Naive*

The primary efficacy outcome in DRIVE-FORWARD and DRIVE-AHEAD was the proportions of patients with HIV-1 RNA < 50 copies/mL at week 48, as determined by the FDA-defined snapshot algorithm. Under this approach, all missing data were treated as failures regardless of the reason.

Secondary outcomes of interest were identified in the review protocol (Table 3): virologic failure, CD4 cell count, drug resistance, adherence, and health-related quality of life (HRQoL). Virologic failure was defined as the proportions of patients with HIV-1 RNA  $\geq$  50 copies/mL at week 48, as determined by the FDA snapshot algorithm. Changes in CD4 cell count from baseline were estimated at week 48 (or most-recent screening visit if baseline values were missing). The magnitude and direction of the CD4 cell count was compared with the baseline value rather than a pre-established cutoff.

Genotypic and phenotypic resistance testing to the study drugs and backbone therapies were performed by a central laboratory. Data were summarized for patients who met the criteria for PDVF and those who discontinued the trial for any reason. Patients were classified as PDVF if they experienced a rebound in HIV-1 RNA  $\geq$  50 copies/mL at any visit after achieving HIV-1 RNA < 50 copies/mL, confirmed HIV-1 RNA  $\geq$  200 copies/mL at week 24 or 36, or (3) confirmed HIV-1 RNA  $\geq$  50 copies/mL at week 48.

Drug adherence was calculated based on a subjective rating method — the Study Medication Diary Cards — which was further validated by the study coordinator for completeness and accuracy. Per cent adherence was calculated by dividing the number of days a patient was “on-therapy” by the number of days the patient should be on therapy. Two definitions of an on-therapy day were used. Partial adherence was assigned to a study day if the patient took at least one tablet from any supplied bottle/container, whereas full adherence was assigned to a study day if the patient took the required number of tablets from each bottle/container. It should be noted that adherence was not regarded as an efficacy outcome, and data were therefore presented descriptively.

One relevant subgroup analysis was pre-planned in both study protocols: primary efficacy outcome by baseline viral load (< 100,000 copies/mL and  $\geq$  100,000 copies/mL). Neither trial assessed HRQoL.

Harms outcomes included the changes from baseline in fasting lipids (LDL, non-HDL, total cholesterol, HDL, and triglycerides) monitoring of all adverse events, and clinical and laboratory tests. An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease as well as worsening of a pre-existing condition that is temporally associated with the study medication or procedure. A serious adverse event (SAE) was any AE that: resulted in death, was life-threatening, resulted in a persistent or significant disability/incapacity, resulted in or prolonged an existing in-patient hospitalization, was a congenital anomaly/birth defect, or was another important medical event. Any incidence of cancer or overdose-associated AE was also considered an SAE. The severity of laboratory AEs was based on the Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria. In DRIVE-AHEAD, three categories of neuropsychiatric AEs (dizziness, sleep disorders, and altered sensorium, e.g., depressed level of consciousness, lethargy, somnolence, syncope) by week 48 constituted the primary safety end point, and an

additional two categories (depression and suicide/self-injury and psychosis/psychotic disorders) were secondary safety end points.

The efficacy and safety assessments described above were carried out at various time points through week 96, and between-treatment comparisons were made at week 96 for the following outcomes: changes from baseline in CD4 cell count, and virologic suppression (HIV-1 RNA < 50 copies/mL) (tested for noninferiority and superiority).

## Treatment-Switch

All efficacy and safety end points in DRIVE-SHIFT were measured at various time points through week 48. Between-treatment comparisons were done at two time points: comparison between the ISG arm receiving DOR/3TC/TDF for weeks 0 to 48 and the DSG arm receiving baseline regimen for weeks 0 to 24 (primary time point), and comparison between the ISG and baseline regimen for the DSG arm at weeks 0 to 24 (secondary time point). The primary outcome in DRIVE-SHIFT was the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48 (ISG) or week 24 (DSG), as determined by the FDA-defined snapshot algorithm. The secondary outcomes of interest for this review included virologic failure, resistance, study drug adherence, and HRQoL. Virologic failure, drug resistance, and adherence were measured in ways identical to those described earlier for the treatment-naive population. Between-treatment comparisons were done for the following outcomes and time points: proportions of patients maintaining virologic suppression in both treatment arms at week 24 (tested for noninferiority and superiority), proportions of patients maintaining virologic suppression between the ISG arm at week 48 and baseline regimen for the DSG arm at week 24 (tested for superiority), proportions of patients with HIV-1 RNA ≥ 50 copies/mL (i.e., virologic failure) between the ISG arm at week 48 and baseline regimen for the DSG arm at week 24, and changes from baseline in CD4 cell count between the DSG arm at week 24 and the ISG arm at weeks 48 and 24.

HRQoL was assessed using the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L), a generic quality-of-life instrument that can be applied to a wide range of health conditions and treatments to capture the net effect of treatment benefits and harms.<sup>33</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”). The EQ-5D-5L index score is generated by applying a multi-attribute utility function to the descriptive system.<sup>33</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>33</sup> The trial reported only VAS data, validation information, and a minimum clinically important difference (MCID), which was not found in the literature for patients with HIV.

Harms outcomes included the monitoring of all AEs, clinical laboratory tests, changes from baseline in fasting lipids, and neuropsychiatric AEs. Between-treatment comparisons were done for changes from baseline in fasting LDL and non-HDL in each treatment arm at week 24.

## Statistical Analysis

### *Statistical Analysis for Efficacy End Points*

All statistical tests were conducted at an alpha level of 0.05 (two-sided) unless otherwise indicated. In all three trials, the primary outcome (difference in proportions between-treatment groups and the associated 95% confidence interval [CI]) was calculated using the



stratum-adjusted Mantel–Haenszel method, with the difference weighted by the harmonic mean of the sample size per arm for each stratum (screening HIV RNA  $\leq$  100,000 or  $>$  100,000 copies/mL for DRIVE-FORWARD and DRIVE-AHEAD and PI use in baseline regimen for DRIVE-SHIFT). The remaining stratification factors, chronic hepatitis co-infection for DRIVE-AHEAD and the use of lipid-lowering therapy for DRIVE-SHIFT, were not expected to be associated with virologic response. Stratification by these factors was therefore not included in the analyses of virologic response.

The choice of noninferiority margin (NIM) in DRIVE-FORWARD and DRIVE-AHEAD was 10 percentage points, whereas the NIM was eight percentage points in DRIVE-SHIFT. The DOR arm in each trial was considered to be noninferior to the comparator arm if the lower bound of the two-sided 95% CI for the primary outcome (difference in the proportion of patients with HIV-1 RNA  $<$  50 copies/mL) was greater than the chosen NIM in each trial. Provided noninferiority was established (DRIVE-FORWARD) or multiplicity criteria were satisfied (DRIVE-AHEAD and DRIVE-SHIFT), the treatment arm was tested for superiority to the respective comparators if the lower bound of the two-sided 95% CI for the difference in response rates was greater than zero.

The treatment difference in changes from baseline in CD4 cell count at time points of interest between the two treatment groups in all trials was estimated using the two-sample *t*-test. Genotypic and phenotypic resistance data from patients with PDVF and those who discontinued for any reason were summarized descriptively, provided they had blood samples available with HIV-1 RNA  $>$  400 copies/mL.

### *Statistical Analysis for Safety End Points*

The analyses of safety end points followed a tiered approach that varied by trial and with respect to the analyses that were performed. The list of safety parameters and analyses strategy for all trials is summarized in Table 6. This review focuses on the notable safety end points described in Table 3.

Tier 1 safety events included the change from baseline in fasting LDL and non-HDL (all trials) and the proportion of patients with neuropsychiatric AEs in three pre-specified categories — dizziness, sleep disorders and disturbances, and altered sensorium (DRIVE-AHEAD only) — by week 48. The change from baseline in fasting lipids at week 48 (week 24 for DRIVE-SHIFT) was analyzed using analysis of covariance models adjusted by baseline lipids level (all trials) and the use of lipid-lowering therapy at study day 1 (DRIVE-SHIFT). In DRIVE-FORWARD, the superiority of DOR over DRV/r in LDL was demonstrated if the mean change from baseline was statistically significantly lower for the former, with a between-group *P* value  $<$  0.04998 (*P* value adjusted for multiple statistical tests). The superiority for non-HDL was tested sequentially at the same alpha level. In DRIVE-SHIFT, after establishing the primary hypothesis of noninferior efficacy, the superiority of switching immediately to DOR over continuing baseline regimens was demonstrated if the mean change from baseline in LDL was statistically significantly lower for the former, with a one-sided between-group *P* value  $<$  0.025. The superiority for non-HDL was tested sequentially at the same alpha level. In all trials, statistical testing was stopped with the first of these tests failing to reach statistical significance and no subsequent tests were considered for statistical significance.

The remaining fasting lipids (all trials) and neuropsychiatric AEs in the depression, suicide/self-injury, psychosis, and psychotic disorders categories (DRIVE-AHEAD) by week 48 were considered tier 2 events. All tier 1 and 2 neuropsychiatric AEs in DRIVE-AHEAD

were analyzed using Miettinen and Nurminen’s method to generate the treatment difference and the associated 95% CI, and *P* values were provided for the tier 1 events only.

**Table 6: Analysis Strategy for Safety Parameters**

Safety Tier	Safety End Point	<i>P</i> Value	95% CI	Descriptive Statistics
<b>Tier 1</b>	Change from baseline in fasting LDL, non-HDL	X	X	X
	Proportion of subjects with neuropsychiatric AEs in the following categories: <sup>a</sup> <ul style="list-style-type: none"> <li>• Dizziness</li> <li>• Sleep disorders and disturbances</li> <li>• Altered Sensorium</li> </ul>	X	X	X
<b>Tier 2</b>	Change from baseline in fasting lipids not classified as Tier 1 (total cholesterol, HDL, triglycerides)		X	X
	Starting lipid-lowering therapy		X	X
	Any AE		X	X
	Any SAE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Time to discontinuation from study due to AE <sup>b</sup>		X	X
	Specific AEs, SOCs, or PDLCs <sup>c</sup> (incidence ≥ 4/1% of subjects in one of the treatment groups)			X
	Proportion of subjects with neuropsychiatric AEs in the following categories: <sup>a</sup> <ul style="list-style-type: none"> <li>• Depression and suicide/self-injury</li> <li>• Psychosis and psychotic disorders</li> </ul>		X	X
<b>Tier 3</b>	Proportion of subjects with one or more neuropsychiatric AEs		X	X
	Specific AEs, SOCs or PDLCs (incidence < 4/1% of subjects in all of the treatment groups)			X
	Change from baseline results (labs, vital signs)			X

AE = adverse event; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; SOC = system organ class; PDL = pre-defined limit of change.

<sup>a</sup> Only applicable to DRIVE-AHEAD.

<sup>b</sup> Only applicable to DRIVE-FORWARD.

<sup>c</sup> Includes only those end points not pre-specified as tier 1 and not already pre-specified as tier-2 end points.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

**Missing Data**

Missing values were of three types:

- Intermittent missing values due to a missed or skipped visit or due to an inadequate sample
- Non-intermittent missing values due to premature discontinuations because of treatment-related reasons such as clinical adverse experience, laboratory abnormalities, and withdrawal due to lack of efficacy (based on HIV-1 RNA results)
- Non-intermittent missing values due to premature discontinuations because of other reasons not related to treatment such as loss to follow-up, protocol violation, consent withdrawal, etc.

The two approaches used to handle missing efficacy values are summarized in Table 7. The primary approach was consistent with the FDA “snapshot” approach, in which all missing data were considered treatment failures regardless of reasons. All non-completers as well as those with an HIV-1 RNA measurement of  $\geq 50$  copies/mL were therefore considered virologic failures. Only patients with an HIV-1 RNA level of  $< 50$  copies/mL within the pre-specified time window of the DB phase were classified as virologic successes. In DRIVE-FORWARD, patients were allowed to switch the study backbone NRTI regimens to manage toxicity; those who switched after week 2 and had HIV-1 RNA  $> 40$  copies/mL at the time of switching were also regarded as a failure at all time points post-switching. The second approach was observed failure (OF), in which non-intermittent missing data for patients who prematurely discontinued treatment due to lack of efficacy were considered failures at time points thereafter. Patients with other reasons for missing data were excluded from the analyses.

For patients who had missing lipid data, the last observation following randomization (or before starting lipid-lowering therapy for those who started lipid-lowering therapy) was carried forward for later time points.

**Table 7: Approaches to Handling Missing Data**

Approaches	Intermittent Missing	Non-Intermittent Missing Not Related to Treatment		Non-Intermittent Missing Related to Treatment	
		Success at Treatment Discontinuation	Failure at Treatment Discontinuation	Treatment Discontinuation Due to Clinical/Lab Adverse Experience	Treatment Discontinuation Due to Lack of Efficacy
<b>OF</b>	Excluded	Excluded	Failure	Excluded	Failure
<b>NC = F</b>	Failure	Failure	Failure	Failure	Failure

F = failure; OF = observed failure; NC = non-completer.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

### Sensitivity Analyses

A sensitivity analysis for the primary efficacy outcome was performed using the OF approach under which non-intermittent missing data for patients who prematurely discontinued their assigned treatment due to lack of efficacy were regarded as failures thereafter.

### Sample Size Calculation

All three trials used an asymptotic method proposed by Farrington and Manning for power calculations. The sample size in DRIVE-FORWARD and DRIVE-AHEAD was chosen to provide 90% power to demonstrate noninferiority of DOR compared with the respective comparator at an overall one-sided 2.5% alpha level for the primary end point — the proportion of patients achieving HIV-1 RNA  $< 50$  copies/mL at Week 48 — assuming a true response rate of 80% for both treatment arms using the FDA snapshot approach. This resulted in 340 patients in each group.

Power estimates for safety end points related to lipid profiles in DRIVE-FORWARD and DRIVE-AHEAD were based on data from a previous study (MK-1439 007, which studied four doses of DOR versus efavirenz, each in combination therapy with Truvada). It was estimated

that with a sample size of 340 patients per treatment arm, the studies had > 99% power to detect a between-treatment difference of 0.43 mmol/L (7.7 mg/dL) and 1.11 mmol/L (20 mg/dL) for LDL and non-HDL, respectively.

In DRIVE-AHEAD, data from a previous study (MK-1439 007) was used to estimate the power to detect between-treatment differences in three pre-specified neuropsychiatric AEs: dizziness, sleep disorders and disturbances, and altered sensorium. The expected frequency for these AEs in the DOR and EFV arms, respectively, were 5% versus 24% for dizziness, 16% versus 29% for sleep disorders and disturbances, and 3% versus 10% for altered sensorium. With 340 patients in each treatment arm, the study had > 99%, 97%, and 95% power, respectively, to detect between-treatment differences in these tier 1 AEs if the proportions of patients with neuropsychiatric AEs were similar to those observed in study MK-1439 007.

The sample size in DRIVE-SHIFT was chosen to provide 80% power to demonstrate noninferiority of switching immediately to DOR compared with continuing baseline regimen at an overall one-sided 2.5% alpha level for the primary end point, the proportion of patients achieving HIV-1 RNA < 50 copies/mL, assuming a true response rate of 85% for both arms. This resulted in randomizing 660 patients in a 2:1 ratio between the immediate and delayed switch arm. The assumed response rate for the delayed switch arm was based on the result from a similar switch study (the SPIRIT study).

Power estimates for safety end points in DRIVE-SHIFT were based on data from the SPIRIT study, in which the estimated between-treatment differences in mean changes in fasting LDL and non-HDL were 0.89 mmol/L (16 mg/dL) and 1.16 mmol/L (21 mg/dL), respectively. With 440 patients in the ISG arm and 220 patients in the DSG arm, the study had an estimated > 99% power to detect a between-treatment difference of 0.89 mmol/L (16 mg/dL) and 1.16 mmol/L (21 mg/dL) for LDL and non-HDL, respectively.

### *Multiplicity*

Multiple statistical testing was carried out in a hierarchical manner, as shown in Table 8. The efficacy and safety end points were tested in a sequential manner. Testing was stopped with the first of these tests failing to reach statistical significance and no subsequent tests were considered statistically significant. The overall one-sided type I error rate in testing these hypotheses was controlled at 2.5%.

In DRIVE-FORWARD, no adjustment for multiplicity was made for the superiority test as noninferiority was confirmed if the data supported superiority due to the principles of closed testing. Two interim analyses were conducted, but these were unlikely to affect the type I error rate for the testing of the primary efficacy hypothesis or secondary safety hypotheses. The first interim analysis of neuropsychiatric AEs was done for making a program decision and was not related to any of the efficacy or safety end points. The second interim analysis was an efficacy analysis, but for the sole purpose of stopping the study in the event of a lack of efficacy. Notably, a small alpha level of 0.0001 was allocated to each interim analysis. Both the primary efficacy hypothesis and secondary safety hypotheses were tested at the two-sided alpha level of 0.049998.

In DRIVE-AHEAD, three interim safety analyses were carried out, and an alpha level of 0.0001 was allocated to each analysis. All safety hypotheses were tested at a one-sided alpha level of 0.02497. However, the primary efficacy hypothesis for noninferiority was tested at an unadjusted one-sided alpha level of 0.025 because no interim efficacy analysis was scheduled.

**Table 8: Statistical Testing Hierarchy for Multiplicity**

DRIVE-FORWARD	DRIVE-AHEAD	DRIVE-SHIFT
Primary efficacy hypothesis (proportion of patients achieving HIV-1 RNA < 50 copies/mL) testing noninferiority at week 48	Primary efficacy hypothesis (proportion of patients achieving HIV-1 RNA < 50 copies/mL) testing noninferiority at week 48	Primary efficacy hypothesis (proportion of patients maintaining HIV-1 RNA < 50 copies/mL) testing noninferiority at study week 48 for the ISG vs. baseline regimen at study week 24 for the DSG
Secondary efficacy hypothesis (proportion of patients achieving HIV-1 RNA < 50 copies/mL) testing superiority at week 48	Primary safety hypothesis testing superiority for neuropsychiatric AEs at week 48: <ul style="list-style-type: none"> <li>• Dizziness</li> <li>• Sleep disorders and disturbances</li> <li>• Altered sensorium</li> </ul>	Secondary safety hypothesis testing superiority (mean change from baseline) for fasting LDL at week 24
Secondary safety hypothesis testing superiority (mean change from baseline) for fasting LDL at week 48	Secondary safety hypothesis testing superiority (mean change from baseline) for fasting LDL at week 48	Secondary safety hypothesis testing superiority (mean change from baseline) for fasting non-HDL at week 24
Secondary safety hypothesis testing superiority (mean change from baseline) for fasting non-HDL at week 48	Secondary safety hypothesis testing superiority (mean change from baseline) for fasting non-HDL at week 48	Secondary efficacy hypothesis (proportion of patients maintaining HIV-1 RNA < 50 copies/mL) testing superiority at study week 48 for the ISG vs. baseline regimen at study week 24 for the DSG
	Secondary efficacy hypothesis (proportion of patients achieving HIV-1 RNA < 50 copies/mL) testing superiority at week 48	

AE = adverse event; DSG = delayed switch group; HDL = high-density lipoprotein cholesterol; ISG = immediate switch group; LDL = low-density lipoprotein cholesterol; RNA = ribonucleic acid.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

### Subgroup Analyses

In DRIVE-FORWARD and DRIVE-AHEAD, results of the efficacy end points were reported by the subgroup relevant for this review — baseline HIV-1 RNA categories (HIV-1 RNA ≤ 100,000 copies/mL, HIV-1 RNA > 100,000 copies/mL). The estimates of between-group treatment difference were reported as a nominal 95% CI unadjusted for stratification factors. No interaction *P* values were reported. The OF approach was used to handle missing values in these subgroup analyses. Subgroup analyses by baseline viral load were not relevant in DRIVE-SHIFT as all enrolled patients were virologically suppressed.

### Analysis Populations

In all included trials, the full-analysis set (FAS) was used as the primary population for the analyses of efficacy end points. The FAS population consisted of all randomized patients who received at least one dose of the study medication and had at least one measurement of the outcome (baseline or post-baseline). Patients in the FAS population were analyzed based on the treatment group to which they were randomized.

Safety analyses in all three trials were done in the “as-treated” population, consisting of all randomized patients who received at least one dose of study medication. Patients were included in the treatment group that corresponded to the medication they actually received.

The per-protocol (PP) population was used in DRIVE-FORWARD and DRIVE-AHEAD to analyze noninferiority of the key efficacy end points/virologic success by week 48. The PP population consisted of a subset of the FAS population that excluded patients with important deviations from the protocol by week 48, including non-compliance with study medication, discontinuation for reasons not related to treatment, and major protocol violations with the potential to affect efficacy.

### Patient Disposition

Patient disposition for the duration of the base study period of the three trials is summarized in Table 8. Approximately 20% to 25% of the patients screened across the trials were not randomized. In DRIVE-FORWARD and DRIVE-AHEAD, the most common reasons for screening failure were resistance to any of the study drugs, screening plasma HIV-1 RNA < 1,000 copies/mL, treatment for HIV not recommended by a physician, and not willing to provide written consent. In DRIVE-SHIFT, the most common reasons for screening failure were resistance to any study drug, and not meeting the inclusion criterion of receiving one of the specified baseline regimens continuously with HIV-1 RNA at undetectable levels for at least six months without prior virologic failure.

Among the treatment-naïve patients, approximately one-quarter of the patients did not complete the base study period of 96 weeks. The most common causes for study discontinuation were AEs, lack of efficacy, and lost to follow-up. More patients receiving DRV and EFV discontinued the study compared with the DOR arm in DRIVE-FORWARD and DRIVE-AHEAD, respectively. A greater proportion of these patients also experienced AEs. The proportion of patients discontinuing the study by week 48 was lower in the treatment-switch study than in the trials of treatment-naïve patients; differences in discontinuation rate and reasons for discontinuation were largely similar between-treatment groups within the trials.

**Table 9: Patient Disposition**

	DRIVE-FORWARD		DRIVE-AHEAD		DRIVE-SHIFT	
	DOR (N = 383)	DRV/r (N = 383)	DOR/3TC/TDF (N = 364)	EFV/FTC/TDF (N = 364)	ISG (N = 447)	DSG (N = 223)
<b>Screened, N</b>	1,027		992		852	
<b>Randomized, N (%)</b>	769 (74.9)		734 (74)		673 (79)	
	385	384	368	366	450	223
<b>Treated, N (%)</b>	766 (99.6)		728 (99.2)		670 (99.6)	
	383 (99.5)	383 (99.7)	364 (98.9)	364 (99.5)	447 (99.3)	223 (100)
<b>Continued/switched treatment at week 24</b>	NA	NA	NA	NA	427 (95.5)	209 (93.7)
<b>Discontinued 0 to 48 weeks, N (%)</b>	56 (14.5)	71 (18.5)	51 (13.9)	61 (16.7)	40 (8.9)	21 (9.4)
Adverse event	4 (1.0)	12 (3.1)	10 (2.7)	23 (6.3)	13 (2.9)	3 (1.3)
Death	1 (0.3)	0 (0.0)	1 (0.3)	3 (0.8)	1 (0.2)	0 (0.0)
Lack of efficacy	12 (3.1)	14 (3.6)	18 (4.9)	10 (2.7)	5 (1.1)	2 (0.9)
Lost to follow-up	17 (4.4)	19 (4.9)	6 (1.6)	7 (1.9)	5 (1.1)	4 (1.8)
Non-compliance	7 (1.8)	4 (1.0)	1 (0.3)	2 (0.5)	0 (0.0)	1 (0.4)
Physician decision	3 (0.8)	3 (0.8)	2 (0.5)	2 (0.5)	4 (0.9)	4 (1.8)
Pregnancy	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	-	-

	DRIVE-FORWARD		DRIVE-AHEAD		DRIVE-SHIFT	
Protocol deviation	1 (0.3)	6 (1.6)	4 (1.1)	2 (0.5)	1 (0.2)	4 (1.8)
Withdrawal by subject	10 (2.6)	13 (3.4)	8 (2.2)	11 (3.0)	11 (2.4)	3 (1.3)
<b>Discontinued 0 to 96 weeks, N (%)<sup>a</sup></b>	91 (23.6)	110 (28.6)	68 (18.5)	88 (24.0)	-	-
Adverse event	6 (1.6)	14 (3.6)	11 (3.0)	26 (7.1)	-	-
Death	3 (0.8)	1 (0.3)	1 (0.3)	4 (1.1)	-	-
Lack of efficacy	21 (5.5)	32 (8.3)	31 (8.4)	23 (6.3)	-	-
Lost to follow-up	28 (7.3)	24 (6.3)	6 (1.6)	8 (2.2)	-	-
Non-compliance	9 (2.3)	6 (1.6)	1 (0.3)	4 (1.1)	-	-
Physician decision	2 (0.5)	4 (1.0)	2 (0.5)	2 (0.5)	-	-
Pregnancy	2 (0.5)	1 (0.3)	2 (0.5)	2 (0.5)	-	-
Protocol deviation	1 (0.3)	6 (1.6)	4 (1.1)	2 (0.5)	-	-
Withdrawal by subject	19 (4.9)	22 (5.7)	10 (2.7)	17 (4.6)	-	-
Completed base study <sup>b</sup>	565 (73.5)		572 (77.9)		609 (90.5)	
	292 (75.8)	273 (71.1)	296 (80.4)	276 (75.4)	407 (90.4)	202 (90.6)
<b>FAS, N</b>	383	383	364	364	447	223
<b>PP, N<sup>c</sup></b>	353	341	338	339	NR	NR
<b>Safety, N (as treated)</b>	383	383	364	364	447	223

3TC = lamivudine; DOR = doravirine; DRV/r = ritonavir-booster darunavir; DSG = delayed switch group; EFV = efavirenz; FAS = full-analysis set; FTC = emtricitabine; ISG = immediate switch group; NA = not applicable; NR = not reported; PP = per-protocol; TDF = tenofovir disoproxil fumarate.

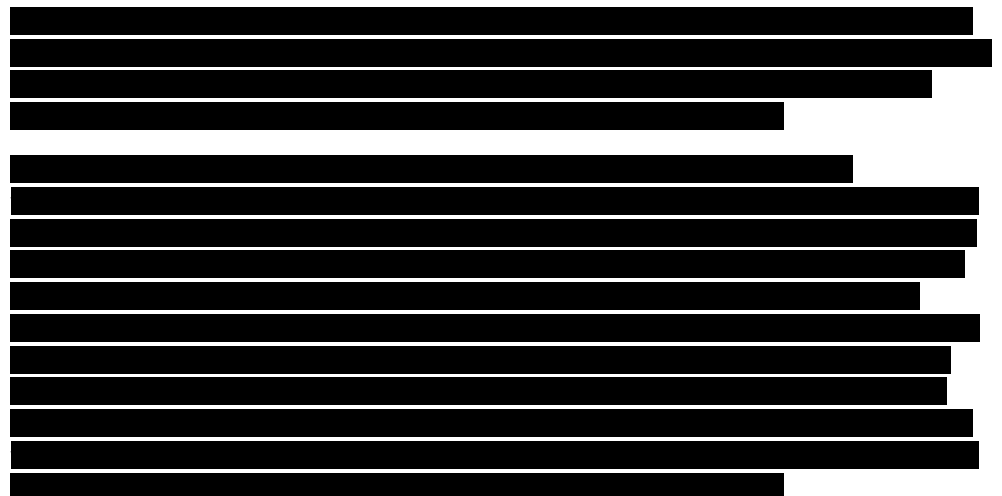
<sup>a</sup> Discontinued base study, i.e., data through week 96.

<sup>b</sup> Week 96 for DRIVE-FORWARD and DRIVE-AHEAD, week 48 for DRIVE-SHIFT.

<sup>c</sup> PP population was relevant to the analyses at 48 weeks only.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

## Exposure to Study Treatments



**Table 10: Exposure to Study Treatments**

Exposure (~ 48 weeks) <sup>a</sup>	DRIVE-FORWARD		DRIVE-AHEAD		DRIVE-SHIFT	
	DOR N = [REDACTED]	DRV/r N = [REDACTED]	DOR/3TC/TDF N = [REDACTED]	EFV/FTC/TDF N = [REDACTED]	ISG DOR/3TC/TDF N = [REDACTED]	DSG DOR/3TC/TDF <sup>b</sup> N = [REDACTED]
Mean duration, days	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Duration range, days	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Exposure (96 weeks)	DRIVE-FORWARD		DRIVE-AHEAD			
	DOR N = [REDACTED]	DRV/r N = [REDACTED]	DOR/3TC/TDF N = [REDACTED]	EFV/FTC/TDF N = [REDACTED]		
Mean duration, days	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		
Duration range, days	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		

3TC = lamivudine; DOR = doravirine; DRV/r = ritonavir-booster darunavir; DSG = delayed switch group; EFV = efavirenz; FTC = emtricitabine; ISG = immediate switch group; TDF = tenofovir disoproxil fumarate.

<sup>a</sup> Data for DRIVE-FORWARD and DRIVE-AHEAD reflect data until the cutoff date, beyond 48 weeks. Approximately [REDACTED] and [REDACTED] of DOR-treated subjects in DRIVE-FORWARD and DRIVE-AHEAD, respectively, had received study medication for > 48 weeks.

<sup>b</sup> Data reported as exposure to DOR/3TC/TDF in the delayed switch group, i.e., exposure during weeks 24 to 28.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

## Critical Appraisal

### Internal Validity

All trials were randomized studies that appear to have used acceptable methods (IVRS/IWRS, computer-generated allocation schedule) to randomize patients to treatment groups. The two DB trials (DRIVE-FORWARD and DRIVE-AHEAD) performed necessary measures to maintain blinding and conceal treatment allocation; all study medications including respective placebos were packaged and supplied in identical containers/bottles. The clinical expert consulted for this review indicated that DRV and EFV are associated with an increased incidence of gastrointestinal and neuropsychiatric AEs, respectively. This is consistent with the relatively high frequency of diarrhea reported among patients receiving DRV/r in DRIVE-FORWARD and dizziness and sleep disorders and disturbances reported among patients receiving EFV/FTC/TDF in DRIVE-AHEAD. It was possible for patients to surmise the greater potential for gastrointestinal and neuropsychiatric side effects with DRV and EFV/FTC/TDF administration, respectively, which might have compromised treatment blinding. Many efficacy and safety outcomes were measured in blood/plasma samples in an objective manner, therefore, reporting bias, if any unblinding occurred, was less likely. However, the possibility remains that ascertainment of treatment allocation influenced patient reporting of subjective outcomes (neuropsychiatric AEs and HRQoL) as well as patients' decisions on whether to remain in the trial, potentially biasing the primary efficacy outcome (given that patients who discontinued the study were considered to have failed to achieve the primary outcome).



In all three studies, the primary efficacy end point was the proportional differences in HIV-1 RNA < 50 copies/mL between the treatment arms. While this is the FDA-recommended efficacy outcome for treatment-naive patients, the end point of interest in switch trials is the proportional difference in HIV-1 RNA  $\geq$  50 copies/mL (not success of < 50 copies/mL as per the manufacturer's analysis).<sup>34</sup> This is because switch trials include patients who are already virologically suppressed. The end point should therefore be focused on patients who lose virologic control post-switching. Even though the proportional difference in HIV-1 RNA  $\geq$  50 copies/mL was measured, this was not part of the statistical testing hierarchy and it was not compared against a pre-specified NIM. The FDA-recommended NIM is four percentage points for HIV-1 RNA  $\geq$  50 copies/mL in switch trials.<sup>34</sup> Therefore, the primary efficacy outcome in DRIVE-SHIFT is inconsistent with FDA recommendations for switch trials. Notably, the manufacturer of DRIVE-SHIFT indicated that the latest issue of FDA guidance for industries<sup>34</sup> with these updated recommendations was published after the trial began.

For all three trials, it is unclear if all of the patients were classified appropriately according to the FDA snapshot algorithm for the outcome of HIV-1 RNA  $\geq$  50 copies/mL, as patients lacking virologic data were not included as failures (assumption of HIV-1 RNA  $\geq$  50 copies/mL). The impact this would have had on the results is uncertain. Other secondary efficacy outcomes as well as safety end points were consistent with FDA guidance and commonly measured in HIV trials. One trial (DRIVE-SHIFT) assessed an HRQoL outcome relevant for this review, but the assessment of the EQ-5D-5L VAS was done without generating an index score, and it provided no supporting evidence for the validity and MCID among HIV patients from the literature.

The statistical analyses plan, including missing data handling (i.e., missing data = failure and missing data = excluded), deriving sample size/power, and adjusting for multiple comparisons was carried out appropriately and generally followed FDA guidance for HIV trials. One notable exception was the handling of missing data in DRIVE-SHIFT. After the initial database lock (dated March 27, 2018) the manufacturer identified a number of patients in the ISG arm with missing HIV-1 RNA data at key efficacy time points. According to the FDA snapshot approach these patients would be counted as treatment failures. The manufacturer discovered additional blood samples were available from the pharmacokinetic and viral resistance samples that could be used to test for HIV-1 RNA (week 24, n = 3; week 48, n = 2). With the addition of sample data for these five patients, the NIM was met for the primary outcome. However, noninferiority was not met based on the data from the initial database lock.

Although subgroup analyses for the DB trials were pre-planned and stratified at randomization, no testing of interaction between subgroups with respect to treatment effect was reported. Additionally, it is unclear if the margin for the overall trial should be used in the evaluation of the subgroups or if subgroup specific margins should have been employed. Indeed, several of the subgroups exceeded the margins, which may be expected given the lack of power within the subgroup analyses. Moreover, multiplicity of testing is still a concern within the subgroups. As a result, over-interpretation of subgroup data should be avoided.

The studies did not use a true intention-to-treat population as several patients were excluded after randomization. However, the numbers are low and are unlikely to affect the study results. Moreover, the DB trials, but not the switch trial, appropriately performed the primary efficacy analysis in a PP population with findings supportive of analysis using the FAS population.

The treatment groups appeared to be generally balanced with respect to baseline characteristics within studies. An exception to this is a lower proportion of patients in the DOR arm with gastrointestinal disorders in DRIVE-FORWARD, and a higher proportion of patients in the ISG arm with immune system disorders, drug hypersensitivity, neoplasms, and psychiatric disorders in DRIVE-SHIFT. Although these differences may have arisen from chance, it is possible that randomization may also have failed. The frequency of dropouts among treatment-naïve patients ranged from 13% to 19% across trials by week 48 and between 18% and 29% by week 96. Patients receiving DOR in both trials had fewer dropouts, in part due to fewer AEs. The higher incidences of dropouts in the comparator arms may bias the results in favour of DOR as dropouts were treated as treatment failures.

In the switch study, the primary efficacy analyses, as well as a number of secondary efficacy and safety analyses, involved comparing the ISG arm at week 48 and the baseline regimen of the DSG arm at week 24. This form of differential follow-up between groups is unusual and the CDR team is uncertain of the impact this has on the results; between-treatment comparisons based on the same duration of follow-up would have more internal validity. While comparisons for efficacy end points were also reported between the treatment arms at week 24, those were not controlled for multiplicity. The FDA guidance document<sup>34</sup> indicates virologic response at 48 weeks is the recommended time point for comparative efficacy determination among patients who are treatment-naïve or who have a well-documented treatment history demonstrating no virologic failure, stating, “Twenty-four weeks of data are appropriate for drugs that have some benefit over existing options (e.g., better efficacy, tolerability, ease of administration), while 48 weeks is recommended for drugs with comparable characteristics to existing options.” However, the expert consulted for this CDR review indicated that, while 24 weeks is a reasonable follow-up period for viral breakthrough after treatment switch, a longer duration of observation may increase the number of AEs identified.

### External Validity

All trials were multinational, enrolling patients from a range of countries across North America, Central and South America, Western Europe, and Asia. Approximately 20% to 25% of the screened patients did not meet the eligibility criteria, primarily due to resistance to any of the study medications (all trials) and having plasma HIV-1 RNA level of < 1,000 copies/mL at screening (treatment-naïve patients). According to the clinical expert consulted for this review, it is standard of care to perform baseline resistance-testing to prevent prescription of an inadequately active ARV, thus exclusion of patients based on resistance-testing does not affect the generalizability of the reviewed trials. Other notable eligibility criteria included not having serious liver or kidney impairments (i.e., not having exclusionary laboratory values), active infection, or acute hepatitis. The results may therefore not be generalized to patients with these conditions. A small proportion of patients (< 5%) were hepatitis B and/or C virus-positive, but the clinical expert consulted by CDR indicated that hepatitis co-infection should not negatively affect the bioavailability of the ARVs or their effectiveness.

The clinical expert consulted for this review indicated that the baseline demographic and clinical characteristics in DRIVE-FORWARD and DRIVE-AHEAD were generally reflective of treatment-naïve patients in a Canadian setting. However, the number of patients with a history of AIDS (9% to 15% across groups) was higher than expected for a treatment-naïve population. The clinical expert consulted by CDR indicated that AIDS is associated with lower CD4 counts and higher viral loads, which may lead to a lower likelihood of virologic

success. A higher percentage of patients in the switch trial had a history of AIDS compared with the treatment-naive patients, likely resulting from their history of living with HIV-1 infection for longer than newly diagnosed treatment-naive patients.

The comparators used in the treatment-naive setting, and in particular, EFV/FTC/TDF used in DRIVE-AHEAD, is infrequently prescribed in contemporary clinical practice according to the expert, and have been largely displaced by first-line therapies that are better-tolerated regimens endorsed by the DHHS,<sup>4</sup> e.g., BIC/TAF/FTC (Biktarvy), EVG/c/TAF/FTC (Genvoya), and DTG/ABC/3TC (Triumeq). EFV and DRV/r are known to cause neuropsychiatric and gastrointestinal adverse effects, respectively, which should be considered when assessing the generalizability of the safety data.

## Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 3). See Appendix 4 for efficacy data from supportive and sensitivity analyses.

### Virologic Response

#### *Treatment-Naive*

Overall, the treatment arms in each trial had comparable efficacy responses at week 48 (Table 11). Approximately 80% of patients achieved the FDA-defined snapshot algorithm of HIV-1 RNA < 50 copies/mL. Treatment differences in DRIVE-FORWARD and DRIVE-AHEAD were 3.9% (95% CI, -1.6 to 9.4) and 3.5% (95% CI, -2.0 to 9.0), respectively. In both cases, the pre-specified NIM of 10% was met, as the lower bound of the 95% CI for treatment differences was above the NIM of -10%. The secondary analyses (PP and sensitivity analysis using the OF approach) supported the primary analyses (Table 27). The proportions of patients with HIV-1 RNA  $\geq$  50 copies/mL using the FDA-defined snapshot approach were 11.2% versus 13.1% between DOR and DRV/r, respectively, in DRIVE-FORWARD, and 10.7% versus 10.2% between DOR/3TC/TDF and EFV/FTC/TDF, respectively, in DRIVE-AHEAD. Approximately 5% to 10% of the patients in the two studies had no virologic data at week 48. The proportion of patients with no virologic data in the EFV arm of DRIVE-AHEAD was noticeably higher compared with the DOR arm (9.1% versus 4.9%), mostly resulting from a disproportionately higher number of patients in the EFV arm discontinuing the study due to AEs or death.

A similar pattern was seen at week 96 (Table 11), where a greater proportion of patients in the DOR arm achieved the FDA-defined snapshot algorithm of HIV-1 RNA < 50 copies/mL. The between-treatment differences in the two trials were 7.1% (95% CI, 0.5 to 13.7) and 3.8% (95%CI, -2.4 to 10.0); and sensitivity analyses using the OF approach supported these findings (Table 29). The proportions of patients with HIV-1 RNA  $\geq$  50 copies/mL using the FDA-defined snapshot approach were 17.2% versus 20.2% between DOR and DRV/r, respectively, in DRIVE-FORWARD, and 15.1% versus 12.1% between DOR/3TC/TDF and EFV/FTC/TDF, respectively, in DRIVE-AHEAD. The proportions of patients with no virologic data at week 96 ranged between 7% and 15%. More patients in the comparator arms of both trials had no virologic data compared with the DOR arm, 13.8% versus 9.8% and 14.3% versus 7.4% in DRIVE-FORWARD and DRIVE-AHEAD, respectively, mostly due to a disproportionately higher percentage of patients in the comparator arms discontinuing the studies.

*Treatment-Switch*

In DRIVE-SHIFT, more than 90% of patients across the treatment arms achieved the FDA-defined snapshot algorithm of HIV-1 RNA < 50 copies/mL (Table 12). The treatment difference between the ISG arm at week 48 and baseline regimen at study week 24 for the DSG arm was 3.8% (95% CI, -7.9 to 0.3), meeting the pre-specified NIM of 8%, as the lower bound of the 95% CI for the between-treatment difference was above the NIM. Of note, noninferiority was not met when data from the initial database lock (dated March 27, 2018) were used for the primary analysis. In this analysis, five patients in the ISG arm had missing HIV-1 RNA data by week 48 (week 24, n = 3; week 48, n = 2) and were analyzed as treatment failures according to the FDA snapshot approach. Based on this, 90.4% and 94.6% of patients achieved HIV-1 RNA < 50 copies/mL with a difference between groups of -4.2% (95% CI, -8.4% to -0.1%) (Appendix 4 Table 28). The NIM was only met following the addition of these missing data into the dataset. The secondary analysis (sensitivity analysis using the OF approach) supported the findings from the primary analyses (Appendix 4 Table 28). The treatment difference between the ISG and baseline regimen (both at week 24) was -0.9% (95%CI, -4.7 to 3.0).

The proportion of patients with HIV 1 RNA ≥ 50 copies/mL using the FDA-defined snapshot approach was < 3% across treatment arms at both time points. Patients with no virologic data at week 24 ranged between 3% and 5% in the ISG and DSG arm, and 7.6% in the ISG arm at week 48.

**Table 11: Virologic Response – Treatment-Naive Patients**

	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR N = 383	DRV/r N = 383	DOR/3TC/TDF N = 364	EFV/FTC/TDF N = 364
<b>48 weeks (primary analysis)</b>				
HIV-1 RNA < 50 copies/mL, n (%) <sup>a</sup>	321 (83.8)	306 (79.9)	307 (84.3)	294 (80.8)
Treatment difference, % (95% CI)	3.9 (-1.6 to 9.4) NI met <sup>b</sup>		3.5 (-2.0 to 9.0) NI met <sup>b</sup>	
HIV-1 RNA ≥ 50 copies/mL, n (%) <sup>a,c</sup>	43 (11.2)	50 (13.1)	39 (10.7)	37 (10.2)
No virologic data	19 (5.0)	27 (7.0)	18 (4.9)	33 (9.1)
Reasons				
Discontinued study due to AE or death <sup>d</sup>	5 (1.3)	11 (2.9)	9 (2.5)	24 (6.6)
Discontinued study for other reasons <sup>e</sup>	11 (2.9)	15 (3.9)	9 (2.5)	8 (2.2)
On study but missing data in window	3 (0.8)	1 (0.3)	0 (0.0)	1 (0.3)
Treatment difference %, (95% CI)	NR		NR	
<b>96 weeks</b>				
HIV-1 RNA < 50 copies/mL, n (%) <sup>a</sup>	N = 379	N = 376	N = 364	N = 364
HIV-1 RNA < 50 copies/mL, n (%) <sup>a</sup>	277 (73.1)	248 (66.0)	282 (77.5)	268 (73.6)
Treatment difference %, (95% CI)	7.1 (0.5 to 13.7)		3.8 (-2.4 to 10.0)	
HIV-1 RNA ≥ 50 copies/mL, n (%) <sup>a,c</sup>	65 (17.2)	76 (20.2)	55 (15.1)	44 (12.1)
Treatment difference %, (95% CI)	NR		NR	
No virologic data	37 (9.8)	52 (13.8)	27 (7.4)	52 (14.3)
Reasons				
Discontinued study due to AE or death <sup>d</sup>	9 (2.4)	14 (3.7)	12 (3.3)	30 (8.2)

	DRIVE-FORWARD		DRIVE-AHEAD	
Discontinued study for other reasons <sup>e</sup>	26 (6.9)	33 (8.8)	13 (3.6)	20 (5.5)
On study but missing data in window	2 (0.5)	5 (1.3)	2 (0.5)	2 (0.5)

3TC = lamivudine; AE = adverse event; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-booster darunavir; EFV = efavirenz; FTC = emtricitabine; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

<sup>a</sup> Snapshot approach under which all missing values were counted as failure.

<sup>b</sup> Noninferiority margin = 10%.

<sup>c</sup> Includes patients who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before the specified time window, patients who discontinued study drug or study before week 48/96 for lack or loss of efficacy, and patients with HIV-1 RNA ≥ 50 copies/mL in the specified time window.

<sup>d</sup> Includes subjects who discontinued because of AEs or death at any time point from day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

<sup>e</sup> Other reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, withdrawal by subject.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

**Table 12: Virologic Response – Treatment-Experienced Patients**

DRIVE-SHIFT					
	Primary time point		Secondary time point		
	ISG week 0 to 48 N = 447	DSG week 0 to 24 N = 223	ISG week 0 to 24 N = 447	DSG week 0 to 24 N = 223	DSG week 24 to 48 N = 209
<b>Proportion of patients with HIV-1 RNA &lt; 50 copies/mL<sup>a</sup></b>					
n/N (%)	406/447 (90.8)	211/223 (94.6)	419/447 (93.7)	211/223 (94.6)	198 (94.7)
Treatment difference %, 95% CI	-3.8 (-7.9 to 0.3) NI met <sup>b</sup>		-0.9 (-4.7 to 3.0)		
<b>Proportion of Patients with HIV-1 RNA ≥ 50 copies/mL<sup>a,c</sup></b>					
n/N (%)	7/447 (1.6)	4/223 (1.8)	8/447 (1.8)	4/223 (1.8)	6 (2.9)
Treatment difference %, 95% CI	-0.2 (-2.5 to 2.1)		-0.0 (-2.3 to 2.3)		
No virologic data	34 (7.6)	8 (3.6)	20 (4.5)	8 (3.6)	5 (2.4)
<b>Reasons</b>					
Discontinued study due to AE or death <sup>d</sup>	14 (3.1)	0	6 (1.3)	0	2 (1.0)
Discontinued study for other reasons <sup>e</sup>	20 (4.5)	8 (3.6)	12 (2.7)	8 (3.6)	3 (1.4)
On study but missing data in window	0	0	2 (0.4)	0	0

AE = adverse event; CI = confidence interval; DSG = delayed switch group; ISG = immediate switch group; RNA = ribonucleic acid.

Note: The DSG continues baseline regimen (ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or non-nucleoside reverse transcriptase inhibitor, each administered with two nucleoside reverse transcriptase inhibitors) until the time of the switch to doravirine/lamivudine/tenofovir disoproxil fumarate once daily at study week 24.

<sup>a</sup> Snapshot approach under which all missing values were counted as failure.

<sup>b</sup> Noninferiority margin 8%.

<sup>c</sup> Includes patients who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before the specified time window, patients who discontinued study drug or study before week 48 for lack or loss of efficacy, and patients with HIV-1 RNA ≥ 50 copies/mL in the specified time window.

<sup>d</sup> Includes subjects who discontinued because of AEs or death at any time point from day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

<sup>e</sup> Other reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, withdrawal by subject.

Source: DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

## CD4 Cell Count

### Treatment-Naive

The mean CD4 cell count at baseline ranged between 411 and 435 cells/mm<sup>3</sup> across the trials (Table 13). In both trials, patients had an increase in CD4 cell count at weeks 48 and 96, regardless of treatment. The mean differences between the treatment arms at week 48 were 7.1 (95% CI, -20.8 to 35.0) and 10.1 (95% CI, -16.1 to 36.3) in DRIVE-FORWARD and DRIVE-AHEAD, respectively. At week 96, the respective treatment differences in the two trials were 17.4 (95% CI, -14.5 to 49.3) and 14.7 (95% CI, -18.7 to 48.2).

### Treatment-Switch

The mean CD4 cell count at baseline ranged from 649 to 665 cells/mm<sup>3</sup> in the two treatment arms (Table 14). The mean differences between the arms at both time points were comparable, albeit numerically greater at the primary time point. The treatment differences at the primary and secondary time points were -4.0 (95% CI, -31.6 to 23.5) and -12.8 (95% CI, -41.1 to 15.4), respectively.

**Table 13: CD4 Cell Count – Treatment-Naive Patients**

	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR N = 383	DRV/r N = 383	DOR/3TC/TDF N = 364	EFV/FTC/TDF N = 364
<b>CD4 cell count (cells/mm<sup>3</sup>)<sup>a</sup></b>				
Baseline, mean (SD)	432.6 (208.4)	411.9 (229.6)	434.9 (217.9)	415.5 (210.6)
<b>48 weeks</b>				
Mean change from baseline (95% CI)	192.7 (171.5 to 213.9)	185.6 (167.5 to 203.6)	198.4 (180.2 to 216.7)	188.4 (169.5 to 207.2)
Mean difference, 95% CI	7.1 (-20.8 to 35.0)		10.1 (-16.1 to 36.3)	
<b>96 weeks</b>				
Mean change from baseline (95% CI)	224.1 (200.8 to 247.4)	206.7 (184.9 to 228.5)	237.7 (214.9 to 260.6)	223.0 (198.4 to 247.6)
Mean difference, 95% CI	17.4 (-14.5 to 49.3)		14.7 (-18.7 to 48.2)	

3TC = lamivudine; AE = adverse event; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-booster darunavir; EFV = efavirenz; FTC = emtricitabine; SD = standard deviation; TDF = tenofovir disoproxil fumarate.

<sup>a</sup> Observed failure approach, i.e., baseline-carry-forward carried forward for subjects who discontinued assigned therapy due to lack of efficacy.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

**Table 14: CD4 Cell Count – Treatment-Experienced Patients**

	DRIVE-SHIFT			
	Primary time point		Secondary time point	
	ISG week 0 to 48 N = 447	DSG week 0 to 24 N = 223	ISG week 0 to 24 N = 447	DSG week 0 to 24 N = 223
<b>CD4 cell count (cells/mm<sup>3</sup>)<sup>a</sup></b>				
Baseline, mean (SD)	664.9 (295.3)	649.9 (279.2)		
Mean change from baseline (95% CI)	13.9 (-2.6 to 30.4)	18.0 (-3.6 to 39.5)	5.1 (-11.8 to 22.1)	18.0 (-3.6 to 39.5)
Mean difference, 95% CI	-4.0 (-31.6 to 23.5)		-12.8 (-41.1 to 15.4)	

CI = confidence interval; DSG = delayed switch group; ISG = immediate switch group; SD = standard deviation.

<sup>a</sup> Observed failure approach, i.e., baseline-carry-forward carried forward for subjects who discontinued assigned therapy due to lack of efficacy.

Source: DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

## Drug Resistance

### Treatment-Naive

Among the patients who met viral resistance-testing criteria, a smaller percentage underwent successful genotypic and phenotypic resistance-testing. Reasons for not performing resistance-testing include limited sample availability (< 400 copies/mL), and other site error (samples not collected [on time or at all] or sent).

Overall, the number of patients with PDVF and those who discontinued without PDVF increased with follow-up duration; the number of patients with a successful resistance test also increased over this period. Likewise, more patients in either arm within the trials developed resistance at week 96 compared with week 48. The incidences of resistance-associated mutations (RAMs), genotypic or phenotypic, were low across treatment arms (< 15 cases in any treatment group) in both trials, and the clinical expert consulted for this review shared this conclusion. There were more cases of genotypic RAMs than phenotypic RAMs, consistent with the notion that not all genotypic RAMs confer phenotypic resistance. Results are summarized in Table 15.

**Table 15: Drug Resistance – Treatment-Naive Patients**

Drug Resistance	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR N = 383	DRV/r N = 383	DOR/3TC/TDF N = 364	EFV/FTC/TDF N = 364
<b>48 weeks</b>				
<b>Patients with PDVF, N</b>	<b>N = 19</b>	<b>N = 24</b>	<b>N = 22</b>	<b>N = 14</b>
Resistance testing completed, N (%)	7 (36.8)	8 (33.3)	13 (59.1)	10 (71.4)
Study drug RAM, N (type)	0 (G) 0 (P)	3 (G) 0 (P)	7 (G) 6 (P)	9 (G) 8 (P)
NRTI RAM, N (type)	1 (G) 0 (P)	1 (G) 0 (P)	7 (G) 5 (P)	5 (G) 4 (P)
<b>Patients who discontinued without PDVF, N</b>	<b>40</b>	<b>53</b>	<b>35</b>	<b>50</b>
Resistance testing completed, N (%)	2 (5.0)	3 (5.7)	10 (28.6)	14 (28.0)
Study drug RAM, N (type)	1 (G) 2 (P)	1 (G) 0 (P)	0 (G) 0 (P)	5 (G) 3 (P)
NRTI drug RAM, N (type)	1 (G) 1 (P)	0 (G) 0 (P)	2 (G) 0 (P)	1 (G) 0 (P)
<b>96 weeks</b>				
<b>Patients with PDVF, N</b>	<b>N = 34</b>	<b>N = 43</b>	<b>N = 34</b>	<b>N = 28</b>
Resistance testing completed, N (%)	11 (32.3)	14 (32.5)	22 (64.7)	16 (57.1)
Study drug RAM, N (type)	1 (G) 1 (P)	5 (G) 0 (P)	7 (G) 6 (P)	12 (G) 9 (P)
NRTI RAM, N (type)	2 (G) 1 (P)	3 (G) 1 (P)	8 (G) 5 (P)	5 (G) 4 (P)
<b>Patients discontinued without PDVF, N</b>	<b>N = 61</b>	<b>N = 71</b>	<b>N = 39</b>	<b>N = 62</b>
Resistance testing completed, N (%)	4 (6.5)	6 (8.4)	13 (33.3)	22 (35.5)
Study drug RAMs, N (type)	1 (G) 2 (P)	3 (G) 0 (P)	1 (G) 0 (P)	7 (G) 4 (P)

3TC = lamivudine; DOR = doravirine; DRV/r = ritonavir-booster darunavir; EFV = efavirenz; FTC = emtricitabine; G = genotypic; P = phenotypic; PDVF = protocol-defined virologic failure; NRTI = nucleoside reverse transcriptase inhibitor; RAM = resistance-associated mutation; TDF = tenofovir disoproxil fumarate.

Notes: Genotypic RAMs include polymorphisms and other mutations that, by themselves, are not considered clinically important with respect to drug resistance and do not confer phenotypic resistance to a specific drug, but are defined by the central laboratory, based on proprietary algorithms, as resistance-associated for the purpose of the table.

Phenotypic viral resistance to any drug was defined by the central laboratory based on the difference (“fold change”) between the half-maximal inhibitory concentration values (IC50) for a subject’s virus in comparison with wild-type virus. No threshold for defining phenotypic resistance to DOR has yet been clinically defined; the central laboratory used a 2.5-fold change in IC50 versus wild-type virus as a broad assay-reproducibility threshold for potential phenotypic resistance to DOR (commonly done for other antiretrovirals in development before sufficient data are available to define a clinically relevant threshold).

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

*Treatment-Switch*

One incidence of genotypic and phenotypic RAM against the background NRTI was found in the DSG arm prior to switching treatment at week 24. No other RAMs were found by week 48 in either arm (Table 16).

**Table 16: Drug Resistance – Treatment-Experienced Patients**

	DRIVE-SHIFT		
	ISG week 0 to 48 N = 447	DSG week 0 to 24 N = 223	DSG week 24 to 48 N = 209
<b>Patients with PDVF</b>	<b>N = 6</b>	<b>N = 1</b>	<b>N = 1</b>
Resistance testing completed, N (%)	3 (50.0)	1 (100.)	0 (0.0)
Study drug RAM, N (type)	0 (G) 0 (P)	0 (G) 0 (P)	
NRTI RAM, N (type)	0 (G) 0 (P)	1 (G) 1 (P)	
<b>Patients who discontinued without PDVF</b>	<b>N = 34</b>	<b>N = 13</b>	<b>N = 6</b>
Resistance testing completed, N (%)	1 (2.9)	2 (15.4)	0 (0.0)
Study drug RAM, N (type)	0 (G) 0 (P)	0 (G) 0 (P)	
NRTI RAM, N (type)	0 (G) 0 (P)	0 (G) 0 (P)	

DSG = delayed switch group; ISG = immediate switch group; G = genotypic; P = phenotypic; PDVF = protocol-defined virologic failure; NRTI = nucleoside reverse transcriptase inhibitor; RAM = resistance-associated mutation.

Notes: Genotypic RAMs include polymorphisms and other mutations that, by themselves, are not considered clinically important with respect to drug resistance and do not confer phenotypic resistance to a specific drug, but are defined by the central laboratory, based on proprietary algorithms, as resistance-associated for the purpose of the table.

Phenotypic viral resistance to any drug was defined by the central laboratory based on the difference (“fold change”) between the half-maximal inhibitory concentration values (IC50) for a subject’s virus in comparison with wild-type virus. No threshold for defining phenotypic resistance to DOR has yet been clinically defined; the central laboratory used a 2.5-fold change in IC50 versus wild-type virus as a broad assay-reproducibility threshold for potential phenotypic resistance to DOR (commonly done for other antiretrovirals in development before sufficient data are available to define a clinically relevant threshold).

Source: DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

**Adherence**

*Treatment-Naive*

Data for per cent adherence are presented in Table 17 using the “full-compliance” definition, under which an “on-therapy” study day was reported if the patient took the required number of tablets from each supplied bottle/container. In each trial, while in the study, per cent adherence between the treatment arms was generally similar; more than 85% patients had an adherence of 90% or higher at both time points. No formal statistical test was completed for these end points.

**Table 17: Treatment Adherence – Treatment-Naive Patients**

Treatment adherence	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR N = 383	DRV/r N = 383	DOR/3TC/TDF N = 364	EFV/FTC/TDF N = 364
<b>Per cent adherence (48 weeks), n (%)<sup>a</sup></b>				
100%	207 (54.0)	223 (58.2)	115 (31.6)	106 (29.1)
99% to 90%	156 (40.7)	143 (37.3)	224 (61.5)	216 (59.3)
89% to 80%	11 (2.9)	9 (2.3)	10 (2.7)	23 (6.3)
79% to 70%	4 (1.0)	3 (0.8)	6 (1.6)	8 (2.2)
< 70%	5 (1.3)	5 (1.3)	9 (2.5)	11 (3.0)
<b>Per cent adherence (96 weeks), n (%)<sup>a</sup></b>				
100%	171 (44.6)	189 (49.3)	90 (24.7)	82 (22.5)



	DRIVE-FORWARD		DRIVE-AHEAD	
99% to 90%	195 (50.9)	179 (46.7)	247 (67.9)	237 (65.1)
89% to 80%	8 (2.1)	7 (1.8)	18 (4.9)	25 (6.9)
79% to 70%	3 (0.8)	3 (0.8)	1 (0.3)	6 (1.6)
< 70%	6 (1.6)	5 (1.3)	8 (2.2)	14 (3.8)

3TC = lamivudine; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate.

<sup>a</sup> Full compliance considers a day within the study an "on-therapy" day only if the subject took the required number of tablets from all bottles/containers provided for this study.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

### Treatment-Switch

Similar to the treatment-naive patients, while in the study, per cent adherence in DRIVE-SHIFT was high and generally similar between-treatment arms by week 48 (Table 18); adherence with the study medication regimen was  $\geq 90\%$  for most participants in the ISG and for the DSG before and after switching to DOR/3TC/TDF. No formal statistical test was completed for these end points.

**Table 18: Treatment Adherence – Treatment-Experienced Patients**

Per cent adherence, n (%) <sup>a</sup>	DRIVE-SHIFT		
	ISG week 0 to 48 N = 447	DSG week 0 to 24 N = 223	DSG week 24 to 48 N = 209
100%	228 (51.0)	158 (70.9)	141 (67.5)
99% to 90%	192 (43.0)	51 (22.9)	60 (28.7)
89% to 80%	7 (1.6)	1 (0.4)	4 (1.9)
79% to 70%	4 (0.9)	2 (0.9)	1 (0.5)
< 70%	16 (3.6)	11 (4.9)	3 (1.4)

DSG = delayed switch group; ISG = immediate switch group

<sup>a</sup> Full compliance, which considers a day within the study an on-therapy day only if the subject took the required number of tablets from all bottles/containers provided for this study.

Source: DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

### Health-Related Quality of Life (EuroQol 5-Dimensions 5-Levels Visual Analogue Survey)

HRQoL, as assessed by the EQ-5D-5L VAS, was measured only in DRIVE-SHIFT. The mean changes from baseline were  $-1.23$  and  $-0.70$  for ISG and DSG, respectively, at week 24 and  $-0.76$  and  $-0.86$  for ISG and DSG, respectively, at week 48. The treatment difference between the ISG and DSG arm was only applicable to week 24 due to different lengths of drug exposure to DOR/3TC/TDF in each treatment group.

**Table 19: Health-Related Quality of Outcomes – Treatment-Experienced Patients**

	DRIVE-SHIFT			
	ISG week 0 to 48 N = 348	DSG week 0 to 48 N = 177	ISG week 0 to 24 N = 364	DSG week 0 to 24 N = 192
EQ-5D VAS <sup>a</sup> change from baseline				
Baseline mean (SD)	85.5 (14.7)	87.3 (11.4)	85.7 (14.2)	87.2 (11.8)
Change from baseline <sup>b</sup> mean (SD)	-0.76 (16.7)	-0.86 (15.2)	-1.23 (15.62)	-0.70 (11.92)
Treatment difference ISG – DSG, mean (95% CI)	NR		-0.54 (-3.07 to 2.00)	

CI = confidence interval; DSG = delayed switch group; EQ-5D = EuroQol 5-Dimensions questionnaire; ISG = immediate switch group; NR = not reported; SD = standard deviation; VAS = visual analogue scale.

Note: This analysis included patients with non-missing patient-reported outcome assessments at baseline and at least one non-missing patient-reported outcome assessment post-baseline.

<sup>a</sup> EQ-5D VAS: range from 0 (worst imaginable health state) to 100 (best imaginable health state).

<sup>b</sup> Mean change from baseline in EQ VAS Score: < 0: worst health status, ≥ 0: same or better health status.

Source: DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

### Subgroup Analyses

Data for subgroup analyses relevant for this review are presented here. Data were available for treatment-naïve patients only, as the switch trial included patients who were virologically suppressed with ART regimens.

Overall, the proportions of patients achieving HIV-1 RNA < 50 copies/mL were numerically smaller for patients with baseline HIV-1 RNA > 100,000 copies/mL than those with baseline HIV-1 RNA ≤ 100,000 copies/mL (Table 20). Overall, between-treatment differences across subgroups ranged between -0.5 and 3.0 percentage points at week 48 and between -0.6 and 6.0 percentage points at week 96.

Virologic success was also measured by background NRTI treatment in DRIVE-FORWARD. Results were consistent with the primary analysis; both groups achieved a similar proportion of virologic success at both time points regardless of background NRTI received (data not presented).

**Table 20: Virologic Response by Subgroups – Treatment-Naïve Patients**

Outcome/subgroup (48 weeks)	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR N = 285	DRV/r N = 282	DOR/3TC/TDF N = 277	EFV/FTC/TDF N = 258
<b>HIV-1 RNA &lt; 50 copies/mL<sup>a</sup></b>				
Baseline plasma HIV-1 RNA ≤ 100,000 copies/mL				
n (%)	257 (90.2)	250 (88.7)	251 (90.6)	235 (91.1)
Treatment difference, % response (95% CI)	1.5 (-3.7 to 6.8)		-0.5 (-5.5 to 4.4)	
Baseline plasma HIV-1 RNA > 100,000 copies/mL	<b>DOR N = 79</b>	<b>DRV/r N = 72</b>	<b>DOR/3TC/TDF N = 69</b>	<b>EFV/FTC/TDF N = 73</b>
n (%)	64 (81.0)	55 (76.4)	56 (81.2)	59 (80.8)
Treatment difference, % response (95% CI)	3.0 (-11.2 to 17.1)		1.0 (-12.4 to 14.3)	
<b>Outcome/subgroup (96 weeks)</b>	<b>DOR N = 264</b>	<b>DRV/r N = 256</b>	<b>DOR/3TC/TDF N = 268</b>	<b>EFV/FTC/TDF N = 248</b>

	DRIVE-FORWARD		DRIVE-AHEAD	
<b>HIV 1 RNA &lt; 50 Copies/mL<sup>a</sup></b>				
Baseline HIV-1 RNA ≤ 100,000 copies/mL				
n (%)	226 (85.6)	204 (79.7)	233 (86.9)	217 (87.5)
Treatment difference, % response (95% CI)	6.0 (-0.6 to 12.6)		-0.6 (-6.4 to 5.3)	
Baseline HIV-1 RNA > 100,000 copies/mL	<b>DOR N = 78</b>	<b>DRV/r N = 66</b>	<b>DOR/3TC/TDF N = 69</b>	<b>EFV/FTC/TDF N = 64</b>
n (%)	51/78 (65.4)	43/66 (65.2)	49/69 (71.0)	51/64 (79.7)
Treatment difference, % response (95% CI)	-1.1 (-17.6 to 15.3)		-8.1 (-22.9 to 6.7)	

3TC = lamivudine; ABC = abacavir; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

<sup>a</sup> Observed failure approach, i.e., baseline-carry-forward carried forward for subjects who discontinued assigned therapy due to lack of efficacy.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

Change from baseline in CD4 cell counts between-treatment arms varied by subgroups in the DRIVE-AHEAD (Table 21). At both time points post-baseline, patients with baseline plasma HIV-1 RNA > 100,000 copies/mL in the DOR/3TC/TDF arm had a numerically greater CD4 cell count compared with the EFV/FTC/TDF arm. CD4 cell counts across subgroups within the trials generally increased over time, although the magnitude of increase was greater among patients with baseline plasma HIV-1 RNA ≤ 100,000 copies/mL.

**Table 21: CD4 Cell Count by Subgroups – Treatment-Naive Patients**

	DRIVE-FORWARD		DRIVE-AHEAD	
<b>Outcome/subgroup (48 weeks)</b>	<b>DOR N = 284</b>	<b>DRV/r N = 280</b>	<b>DOR/3TC/TDF N = 275</b>	<b>EFV/FTC/TDF N = 256</b>
<b>CD4 cell count (cells/mm<sup>3</sup>)<sup>a</sup></b>				
Baseline plasma HIV-1 RNA ≤ 100,000 copies/mL				
Baseline mean	452.9	448.1	462.6	444.5
Mean change from baseline (95% CI)	182.3 (158.4 to 206.3)	171.3 (151.7 to 190.9)	186.8 (167.5 to 206.1)	186.7 (164.8 to 208.6)
Mean difference (95% CI)	11.0 (-19.9 to 41.9)		0.1 (-29.0 to 29.1)	
Baseline plasma HIV-1 RNA > 100,000 copies/mL	<b>DOR N = 79</b>	<b>DRV/r N = 72</b>	<b>DOR/3TC/TDF N = 69</b>	<b>EFV/FTC/TDF N = 73</b>
Baseline mean	362.6	260.8	319.5	308.4
Mean change from baseline (95% CI)	229.9 (184.5 to 275.3)	239.0 (195.2 to 282.9)	244.7 (196.7 to 292.8)	194.1 (156.4 to 231.7)
Mean difference (95% CI)	-9.1 (-71.9 to 53.7)		50.7 (-9.5 to 110.8)	
<b>Outcome/subgroup (96 weeks)</b>				
Baseline HIV-1 RNA ≤ 100,000 copies/mL	<b>DOR N = 264</b>	<b>DRV/r N = 259</b>	<b>DOR/3TC/TDF N = 269</b>	<b>EFV/FTC/TDF N = 247</b>
Baseline mean	448.8	443.7	464.2	440.2
Mean change from baseline (95%CI)	222.5 (196.0 to 248.9)	201.0 (177.4 to 224.6)	222.9 (200.4 to 245.4)	223.1 (194.3 to 251.8)
Mean difference (95% CI)	21.5 (-13.9, 56.9)		-0.2 (-36.3 to 35.9)	
Baseline HIV-1 RNA > 100,000 copies/mL	<b>DOR N = 78</b>	<b>DRV/r N = 67</b>	<b>DOR/3TC/TDF N = 68</b>	<b>EFV/FTC/TDF N = 64</b>
Baseline mean	364.6	256.1	323.9	310.8

	DRIVE-FORWARD		DRIVE-AHEAD	
Mean change from baseline (95%CI)	229.6 (179.4 to 279.8)	225.3 (169.8 to 280.7)	296.5 (226.6 to 366.3)	222.8 (177.0 to 268.5)
Mean difference (95% CI)	4.3 (-69.7 to 78.4)		73.7 (-10.1 to 157.5)	

3TC = lamivudine; ABC = abacavir; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

\* Observed failure approach, i.e., baseline-carry-forward carried forward for subjects who discontinued assigned therapy due to lack of efficacy.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

## Harms

Only those harms identified in the review protocol (Table 3) are reported below. See Table 23 for detailed harms data. Harms data through weeks 96 and 48 are provided for treatment-naïve and treatment-switch patients, respectively.

### Adverse Events

#### *Treatment-Naïve*

The overall frequency of AEs ranged between 82% and 94% across trials. The majority of these events were mild to moderate in intensity. The most common AEs across treatment groups included diarrhea, headache, upper respiratory tract infection (URTI), nausea, viral URTI, nasopharyngitis, pharyngitis, fatigue, back pain, bronchitis, cough, syphilis, upper abdominal pain, insomnia, dizziness, somnolence, abnormal dreams, and rash-related events. AEs that occurred at noticeably different frequencies between-treatment groups ( $\geq 5\%$ ) included diarrhea (17.0% versus 23.8%), URTI (13.3% versus 7.8%), and back pain (7.3% versus 2.9%) in DRIVE-FORWARD and dizziness (10.2% versus 38.2%), abnormal dreams (4.9% versus 12.1%), and rash-related events (7.1% versus 18.1%) in DRIVE-AHEAD.

#### *Treatment-Switch*

In the switch study, patients in the ISG arm experienced more AEs compared with the baseline regimen at week 24 for the DSG arm (68.9% versus 52.5%, respectively). The most common AEs between the treatment groups across time points included diarrhea, nasopharyngitis, back pain, and headache.

### Serious Adverse Events

Overall, less than 10% of treatment-naïve patients experienced one or more SAEs through week 96, with similar proportions across treatment groups within each trial. Gastrointestinal disorders and infection and infestations constituted the majority of the SAEs.

The percentage of patients in DRIVE-SHIFT that experienced SAEs by week 48 did not exceed 5% at any time point. Infection and infestations constituted the majority of the SAEs.

### Withdrawals Due to Adverse Events

The proportions of treatment-naïve patients with withdrawal due to adverse events (WDAEs) were generally low across trials ( $< 8\%$ ). Patients in the EFV/FTC/TDF arm of DRIVE-AHEAD had more WDAEs compared with the DOR/3TC/TDF arm (7.4% versus 3.0%). In the switch trial, less than 4% of patients in either arm had WDAEs at any time point by week 48.

### Mortality

The number of deaths reported here includes those who died during and after the treatment phase of the base study. A total of 11 deaths were reported in DRIVE-FORWARD and DRIVE-AHEAD. The primary causes of deaths were natural causes, pulmonary embolism, myocardial infarction, cardiac failure, Hodgkin’s disease, suicide, cocaine overdose, road accident, or unknown. None of the reported deaths with known causes were deemed to be related to the study drug according to the site investigator. In DRIVE-SHIFT, two reported cases of death occurred, both in the ISG arm, one of which (a myocardial infarction) was considered to be related to the study drug, although no confirmatory diagnosis (diagnosis by a medical professional or autopsy) was done.

Of note, all reported cases of death from cardiac events occurred in patients receiving DOR.

**Table 22: Harms in Treatment-Naive Patients (96 Weeks)**

AEs	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR N = 383	DRV/r N = 383	DOR/3TC/TDF N = 364	EFV/FTC/TDF N = 364
Subjects with > 0 AEs, N (%)	324 (84.6)	317 (82.8)	321 (88.2)	339 (93.1)
Most common AEs <sup>a</sup>				
Abdominal pain upper	20 (5.2)	13 (3.4)	10 (2.7)	6 (1.6)
Diarrhea	65 (17.0)	91 (23.8)	48 (13.2)	58 (15.9)
Nausea	45 (11.7)	52 (13.6)	31 (8.5)	42 (11.5)
Vomiting	-	-	19 (5.2)	29 (8.0)
Fatigue	34 (8.9)	23 (6.0)	22 (6.0)	24 (6.6)
Bronchitis	23 (6.0)	29 (7.6)	11 (3.0)	15 (4.1)
Syphilis	22 (5.7)	23 (6.0)	18 (4.9)	14 (3.8)
Nasopharyngitis	-	-	50 (13.7)	43 (11.8)
Pharyngitis	-	-	31 (8.5)	20 (5.5)
URTI	51 (13.3)	30 (7.8)	41 (11.3)	29 (8.0)
Back pain	28 (7.3)	11 (2.9)	18 (4.9)	18 (4.9)
Dizziness	20 (5.2)	19 (5.0)	37 (10.2)	139 (38.2)
Somnolence	3 (0.8)	6 (1.6)	13 (3.6)	28 (7.7)
Abnormal dreams	5 (1.3)	3 (0.8)	18 (4.9)	44 (12.1)
Insomnia	18 (4.7)	20 (5.2)	25 (6.9)	38 (10.4)
Headache	57 (14.9)	46 (12.0)	57 (15.7)	56 (15.4)
Cough	23 (6.0)	10 (2.6)	22 (6.0)	20 (5.5)
Rash-related event	36 (9.4)	37 (9.7)	26 (7.1)	66 (18.1)
<b>SAEs</b>				
Subjects with > 0 SAEs, N (%)	27 (7.0)	33 (8.6)	21 (5.8)	30 (8.2)
Most common SAEs by SOC <sup>b</sup>				
Cardiac disorders	-	-	2 (0.5)	0 (0.0)
Gastrointestinal disorders	4 (1.0)	3 (0.8)	1 (0.3)	1 (0.3)
General disorders and administration site conditions	1 (0.3)	2 (0.5)	1 (0.3)	1 (0.3)
Hepatobiliary disorders	-	-	2 (0.5)	0

	DRIVE-FORWARD		DRIVE-AHEAD	
Infections and infestations	9 (2.3)	12 (3.1)	10 (2.7)	12 (3.3)
Injury, poisoning, and procedural complications	3 (0.8)	6 (1.6)	2 (0.5)	3 (0.8)
Musculoskeletal and connective tissue disorders	2 (0.5)	3 (0.8)	0 (0.0)	2 (0.5)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.5)	3 (0.8)	3 (0.8)	4 (1.1)
Nervous system disorders	1 (0.3)	4 (1.0)	1 (0.3)	1 (0.3)
Psychiatric disorders	2 (0.5)	2 (0.5)	1 (0.3)	2 (0.5)
Renal and urinary disorders	-	-	0 (0.0)	2 (0.5)
Skin and subcutaneous tissue disorders	-	-	1 (0.3)	3 (0.8)
Respiratory, thoracic, and mediastinal disorders	1 (0.3)	3 (0.8)	0 (0.0)	1 (0.3)
<b>WDAEs</b>				
Stopped treatment due to AEs, N (%)	6 (1.6)	13 (3.4)	11 (3.0)	27 (7.4)
Drug-related AEs	5 (1.3)	8 (2.1)	8 (2.2)	24 (6.6)
WDAEs	0 (0.0)	3 (0.8)	2 (0.5)	4 (1.1)
<b>DEATHS</b>				
Number of deaths, N (%)	3 (0.8)	2 (0.5)	2 (0.5)	4 (1.1)
<b>NOTABLE HARMS</b>				
Neuropsychiatric AEs	60 (15.7)	72 (18.8)	96 (26.4)	213 (58.5)
Dizziness	20 (5.2)	19 (5.0)	37 (10.2)	139 (38.2)
Sleep disorders and disturbances	34 (8.9)	30 (7.8)	51 (14.0)	100 (27.5)
Altered sensorium	5 (1.3)	18 (4.7)	18 (4.9)	31 (8.5)
Depression and suicide/self-injury	12 (3.1)	22 (5.7)	19 (5.2)	27 (7.4)
Psychosis and psychotic disorders	1 (0.3)	1 (0.3)	2 (0.5)	5 (1.4)
Psychiatric disorders (SOC)	65 (17.0)	65 (17.0)	79 (21.7)	136 (37.4)
Cardiac disorders (SOC)	9 (2.3)	8 (2.1)	9 (2.5)	5 (1.4)
Hypertension	7 (1.8)	5 (1.3)	17 (4.7)	6 (1.6)
Skin and subcutaneous tissue disorders (SOC)	71 (18.5)	69 (18.0)	81 (22.3)	108 (29.7)
Rash-related event	36 (9.4)	37 (9.7)	26 (7.1)	66 (18.1)
Renal and urinary disorders (SOC)	12 (3.1)	11 (2.9)	12 (3.3)	10 (2.7)
DILI <sup>c</sup>	1 (0.3)	0	3 (0.8)	1 (0.3)
<b>CHEMISTRY<sup>d</sup></b>				
Creatinine (mg/dL)				
Grade 2: > 1.3 to 1.8 x ULN or increase of > 0.3 mg/dL above baseline	15/380 (3.9)	22/378 (5.8)	12/363 (3.3)	6/359 (1.7)
Grade 3: > 1.8 to < 3.5 x ULN or increase of 1.5 to < 2.0 x above baseline	11/380 (2.9)	15/378 (4.0)	10/363 (2.8)	5/359 (1.4)
Aspartate aminotransferase (IU/L)				
Grade 1: 1.25 to < 2.5 x ULN	39/380 (10.3)	36/378 (9.5)	39/363 (10.7)	51/359 (14.2)
Grade 2: 2.5 to < 5.0 x ULN	19/380 (5.0)	14/378 (3.7)	11/363 (3.0)	9/359 (2.5)
Grade 3: 5.0 to < 10.0 x ULN	6/380 (1.6)	8/378 (2.1)	2/363 (0.6)	11/359 (3.1)
> 2.5 to 5.0 x baseline	30/380 (7.9)	23/378 (6.1)	25/363 (6.9)	47/359 (13.1)
> 5.0 x baseline	17/380 (4.5)	14/378 (3.7)	10/363 (2.8)	15/359 (4.2)

	DRIVE-FORWARD		DRIVE-AHEAD	
Alanine aminotransferase (IU/L)				
Grade 1: 1.25 to < 2.5 x ULN	52/380 (13.7)	30/378 (7.9)	46/363 (12.7)	70/359 (19.5)
Grade 2: 2.5 to < 5.0 x ULN	14/380 (3.7)	9/378 (2.4)	16/363 (4.4)	15/359 (4.2)
Grade 3: 5.0 to < 10.0 x ULN	5/380 (1.3)	6/378 (1.6)	3/363 (0.8)	7/359 (1.9)
Grade 4: ≥ 10.0 x ULN	1/380 (0.3)	4/378 (1.1)		
> 2.5 to 5.0 x baseline	33/380 (8.7)	20/378 (5.3)	30/363 (8.3)	55/359 (15.3)
> 5.0 x baseline	15/380 (3.9)	15/378 (4.0)	20/363 (5.5)	28/359 (7.8)

3TC = lamivudine; ABC = abacavir; AE = adverse event; ART = antiretroviral therapy; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; IU = international unit; SAE = serious adverse event; SOC = system organ class; TDF = tenofovir disoproxil fumarate; DILI = drug-induced liver injury; URTI = upper respiratory tract infection; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.

<sup>a</sup> Frequency ≥ 5% in one or more treatment groups.

<sup>b</sup> Incidence > 2 in one or more treatment groups.

<sup>c</sup> DILI: alanine aminotransferase or aspartate aminotransferase ≥ 3 × ULN plus bilirubin ≥ 2 × ULN and alkaline phosphatase < 2 × ULN.

<sup>d</sup> For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only patients with a worsened grade from baseline were included. A patient was listed with a Grade X event if his/her highest grade during treatment was X.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

**Table 23: Harms in Treatment-Experienced Patients (≤ 48 Weeks)**

	DRIVE-SHIFT			
AEs	DOR/3TC/TDF ISG weeks 0 to 24 N = 447	Baseline regimen DSG weeks 0 to 24 N = 223	DOR/3TC/TDF DSG weeks 24 to 48 N = 209	DOR/3TC/TDF ISG weeks 0 to 48 N = 447
Subjects with > 0 AEs, N (%)	308 (68.9)	117 (52.5)	126 (60.3)	359 (80.3)
Most common AEs <sup>a</sup>				
Diarrhea	20 (4.5)	5 (2.2)	9 (4.3)	31 (6.9)
Nasopharyngitis	33 (7.4)	12 (5.4)	9 (4.3)	45 (10.1)
Back pain	9 (2.0)	4 (1.8)	1 (0.5)	23 (5.1)
Headache	29 (6.5)	5 (2.2)	14 (6.7)	39 (8.7)
<b>SAEs</b>				
Subjects with > 0 SAEs, N (%)	13 (2.9)	8 (3.6)	4 (1.9)	22 (4.9)
Most common SAEs by SOC <sup>b</sup>				
Cardiac disorders	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)
Infections and infestations	1 (0.2)	4 (1.8)	1 (0.5)	4 (0.9)
Investigations	3 (0.7)	0 (0.0)	0 (0.0)	7 (1.6)
Nervous system disorders	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)
Psychiatric disorders	2 (0.4)	1 (0.4)	0 (0.0)	2 (0.4)
Renal and urinary disorders	0 (0.0)	2 (0.9)	1 (0.5)	1 (0.2)
<b>WDAEs</b>				
Discontinued drug due to AEs, N (%)	11 (2.5)	1 (0.4)	4 (1.9)	15 (3.4)
Drug-related AEs	7 (1.6)	0 (0.0)	4 (1.9)	9 (2.0)
WDAEs	4 (0.9)	1 (0.4)	1 (0.5)	6 (1.3)
<b>Deaths</b>				
Number of deaths, N (%)	0	0 (0.0)	0	2 (0.4)
<b>Notable Harms</b>				
Psychiatric disorders (SOC)	45 (10.1)	10 (4.5)	15 (7.2)	59 (13.2)
Dizziness	10 (2.2)	0 (0.0)	2 (1.0)	13 (2.9)
Sleep Disorders	7 (1.6)	0 (0.0)	4 (1.9)	9 (2.0)
Cardiac disorders (SOC)	5 (1.1)	1 (0.4)	2 (1.0)	7 (1.6)

DRIVE-SHIFT				
Hypertension	1 (0.2)	3 (1.3)	0 (0.0)	7 (1.6)
Skin and subcutaneous tissue disorders (SOC)	34 (7.6)	9 (4.0)	14 (6.7)	54 (12.1)
Rash-related event	12 (2.7)	2 (0.9)	3 (1.4)	18 (4.0)
Renal and urinary disorders (SOC)	12 (2.7)	4 (1.8)	3 (1.4)	20 (4.5)
DILI <sup>c</sup>	0	0	0	0
<b>CHEMISTRY<sup>d</sup></b>				
Creatinine (mg/dL)				
Grade 1: 1.1 to 1.3 x ULN	1 /444 (0.2)	1/221 (0.5)	1/208 (0.5)	1/444 (0.2)
Grade 2: > 1.3 to 1.8 x ULN or Increase of > 0.3 mg/dL above baseline	6/444 (1.4)	1/221 (0.5)	2/208 (1.0)	12/444 (2.7)
Grade 3: > 1.8 to < 3.5 x ULN or increase of 1.5 to < 2.0 x above baseline	2/444 (0.5)	1/221 (0.5)	1/208 (0.5)	4/444 (0.9)
Grade 4: ≥ 3.5 x ULN or Increase of ≥ 2.0 x above baseline	2/444 (0.5)	0/221 (0.0)	0/208 (0.0)	2/444 (0.5)
Aspartate aminotransferase (IU/L)				
Grade 1: 1.25 to <2.5 x ULN	37/444 (8.3)	7/221 (3.2)	11/208 (5.3)	53/444 (11.9)
Grade 2: 2.5 to <5.0 x ULN	8/444 (1.8)	1/221 (0.5)	6/208 (2.9)	13/444 (2.9)
Grade 3: 5.0 to <10.0 x ULN	2/444 (0.5)	0/221 (0.0)	1/208 (0.5)	4/444 (0.9)
Grade 4: ≥ 10.0 x ULN	0/444 (0.0)	0/221 (0.0)	1/208 (0.5)	0/444 (0.0)
> 2.5 to 5.0 x baseline	17/444 (3.8)	2/221 (0.9)	11/208 (5.3)	33/444 (7.4)
> 5.0 x baseline	7/444 (1.6)	1/221 (0.5)	5/208 (2.4)	13/444 (2.9)
Alanine aminotransferase (IU/L)				
Grade 1: 1.25 to < 2.5 x ULN	55 /444 (12.4)	7/221 (3.2)	28/208 (13.5)	74/444 (16.7)
Grade 2: 2.5 to < 5.0 x ULN	11/444 (2.5)	2/221 (0.9)	8/208 (3.8)	19/444 (4.3)
Grade 3: 5.0 to < 10.0 x ULN	3/444 (0.7)	0/221 (0.0)	1/208 (0.5)	5/444 (1.1)
Grade 4: ≥ 10.0 x ULN	0/444 (0.0)	0/221 (0.0)	2/208 (1.0)	0/444 (0.0)
> 2.5 to 5.0 x baseline	46/444 (10.4)	3/221 (1.4)	20/208 (9.6)	66/444 (14.9)
> 5.0 x baseline	15/444 (3.4)	3/221 (1.4)	10/208 (4.8)	23/444 (5.2)

3TC = lamivudine; AE = adverse event; DILI = drug-induced liver injury; DOR = doravirine; DSG = delayed switch group; ISG = immediate switch group; IU = international unit; SOC = system organ class; SAE = serious adverse event; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.

<sup>a</sup> Frequency ≥ 5% in one or more treatment groups.

<sup>b</sup> Incidence > 2 in one or more treatment groups.

<sup>c</sup> DILI: alanine aminotransferase or aspartate aminotransferase ≥ 3 × ULN plus bilirubin ≥ 2 × ULN and alkaline phosphatase < 2 × ULN.

<sup>d</sup> For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. Only patients with a worsened grade from baseline were included. A patient was listed with a Grade X event if his/her highest grade during treatment was X.

Source: DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

## Notable Harms

### Lipid Profile

All three trials measured lipid profiles, of which changes from baseline in fasting LDL and fasting non-HDL at week 48 (DRIVE-FORWARD and DRIVE-AHEAD) or week 24 (DRIVE-SHIFT) were part of the statistical testing hierarchy. Overall, baseline mean levels for each type of lipid were balanced between the treatment groups across trials, with the exception of



fasting triglycerides in DRIVE-AHEAD, which were higher in the DOR/3TC/TDF arm than in the EFV/FTC/TDF arm (199.5 mg/dL versus 123.0 mg/dL).

Among treatment-naïve patients (Table 24), fasting LDL and non-HDL levels were decreased in the DOR arms and increased in their respective comparator arms at week 48 in DRIVE-FORWARD and DRIVE-AHEAD; the mean differences for change from baseline in fasting LDL between the treatment arms (95% CI) were -14.6 mg/dL (-18.1 to -11.1) and -10.0 mg/dL (-13.5 to -6.5), respectively;  $P < 0.0001$  in both cases. For change from baseline in non-HDL, the mean differences between the treatment arms were -19.3 mg/dL (95% CI, -23.3 to -15.3) and -17.02 mg/dL (95% CI, -20.9 to -13.2), respectively;  $P$  value  $< 0.0001$  in both cases. Between-treatment differences for fasting total cholesterol and fasting triglycerides followed a similar pattern, with decreases in DOR arms and increases in comparator arms. Changes from baseline in fasting HDL increased in both treatment groups, although a numerically greater increase occurred in the EFV/FTC/TDF arm in DRIVE-AHEAD. Data at week 96 reflected a similar pattern, where patients receiving DOR showed greater improvement in lipid profiles compared with the respective comparator arm (Table 25).

Among treatment-switch patients, those in the ISG arm had a numerically greater decrease from baseline in fasting LDL and non-HDL at week 24 compared with the DSG arm; mean difference -15.3 mg/dL (95% CI, -18.9 to -1.6) and -23.9 mg/dL (95%CI, -28.1 to -19.6), respectively; no  $P$  value was reported in either case. All statistical comparisons related to lipid profile were done in a subset of patients on a ritonavir-boosted PI regimen (termed ritonavir-boosted PI strata), as the majority (approximately 70%) of the participants in DRIVE-SHIFT were on this regimen at baseline. At week 24, patients in the ISG arm had a statistically significantly greater change from baseline in fasting LDL and non-HDL compared with the DSG arm; between-treatment differences (95% CI) were -14.65 mg/dL (-18.92 to -10.38) and -23.03 mg/dL (-28.00 to -18.05), respectively;  $P$  value  $< 0.0001$  in both cases. Data for the full available sample set are provided in Table 24. A similar pattern was found for fasting cholesterol, triglycerides, and HDL; patients in the ISG arm had a numerically greater improvements in lipid levels from baseline compared with the DSG arm.

**Table 24: Harms – Lipid Profile in All Patients (≤ 48 Weeks)**

	DRIVE-FORWARD		DRIVE-AHEAD		DRIVE-SHIFT	
	DOR N = 383	DRV/r N = 383	DOR/3TC/TDF N = 364	EFV/FTC/TDF N = 364	ISG Week 24 N = 447	DSG Week 24 N = 223
<b>Change from baseline in fasting LDL (mg/dL)</b>	<b>N = 326</b>	<b>N = 318</b>	<b>N = 330</b>	<b>N = 305</b>	<b>N = 371</b>	<b>N = 180</b>
Baseline mean	91.1	91.8	92.0	90.8	112.8	110.2
Mean change (SD)	-4.51 (20.64)	9.92 (27.31)	-1.58 (22.12)	8.74 (25.54)	-18.19 (24.33)	-1.81 (26.36)
Mean difference (95% CI)	-14.61 (-18.15 to -11.06)		-10.01 (-13.53 to -6.49)		-15.29 (-18.99 to -11.59)	
P value	< 0.0001		< 0.0001		NR	
<b>Change From baseline in fasting non-HDL (mg/dL)</b>	<b>N = 329</b>	<b>N = 325</b>	<b>N = 333</b>	<b>N = 314</b>	<b>N = 386</b>	<b>N = 191</b>
Baseline mean	113.3	114.4	115.2	114.8	143.1	139.1
Mean change (SD)	-5.30 (23.28)	13.75 (31.08)	-3.83 (22.59)	13.26 (28.76)	-26.17 (29.84)	-0.55 (29.30)
Mean difference (95% CI)	-19.34 (-23.33 to -15.35)		-17.02 (-20.89 to -13.16)		-23.90 (-28.14 to -19.65)	
P value	< 0.0001		< 0.0001		NR	
<b>Change from baseline in fasting cholesterol (mg/dL)</b>	<b>N = 329</b>	<b>N = 325</b>	<b>N = 333</b>	<b>N = 314</b>	<b>N = 386</b>	<b>N = 191</b>
Baseline mean	156.9	157.7	157.4	156.2	193.6	189.0
Mean change (SD)	-1.37 (25.47)	17.90 (33.95)	-1.97 (25.67)	21.77 (30.74)	-28.80 (31.63)	0.51 (28.78)
Mean difference (95% CI)	-19.50 (-23.82 to 15.17)		-23.44 (-27.57 to -19.32)		-27.34 (-31.72 to -22.96)	
P value	NPS		NPS		NR	
<b>Change from baseline in fasting triglycerides (mg/dL)</b>	<b>N = 329</b>	<b>N = 325</b>	<b>N = 333</b>	<b>N = 314</b>	<b>N = 386</b>	<b>N = 191</b>
Baseline mean	111.2	117.0	199.5	123.0	155.8	152.7
Mean change (SD)	-3.14 (68.81)	21.97 (92.59)	-12.40 (67.30)	22.01 (93.03)	-41.62 (96.54)	4.49 (113.40)
Mean difference (95% CI)	-27.87 (-38.71 to -17.02)		-35.96 (-47.10 to -24.82)		-44.11 (-57.65 to -30.57)	
P value	NPS		NPS		NR	
<b>Change from baseline in fasting HDL cholesterol (mg/dL)</b>	<b>N = 329</b>	<b>N = 325</b>	<b>N = 333</b>	<b>N = 314</b>	<b>N = 386</b>	<b>N = 191</b>
Baseline mean	43.6	43.3	42.2	41.4	50.5	50.0
Mean change (SD)	3.94 (10.66)	4.15 (11.01)	1.86 (9.59)	8.51 (10.66)	-2.63 (9.86)	1.06 (10.45)
Mean difference (95% CI)	-0.15 (-1.75 to 1.45)		-6.47 (-7.97 to -4.96)		-3.60 (-5.18 to -2.03)	
P value	NPS		NPS		NR	

3TC = lamivudine; ABC = abacavir; AE = adverse event; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; DSG = delayed switch group; EFV = efavirenz; FTC = emtricitabine; HDL = high-density lipoprotein cholesterol; ISG = immediate switch group; LDL = low-density lipoprotein cholesterol; NPS = not pre-specified; NR = not reported; SD = standard deviation; TDF = tenofovir disoproxil fumarate.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report,<sup>7,8</sup> DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

Approximately 2% to 7% of patients in the three studies received (started, stopped, or modified dosage) lipid-lowering therapy. For all trials and time points, the between-treatment differences were small and not meaningful clinically or statistically (data not presented).

**Table 25: Harms – Lipid Profile in Treatment-Naive Patients (96 Weeks)**

	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR	DRV/r	DOR/3TC/TDF	EFV/FTC/TDF
<b>Change from baseline in fasting LDL cholesterol (mg/dL)</b>	<b>N = 325</b>	<b>N = 317</b>	<b>N = 330</b>	<b>N = 306</b>
Baseline mean	91.3	91.9	92.0	90.8
Mean change (SD)	-0.4 (21.4)	14.0 (26.9)	-0.6 (25.6)	10.8 (24.6)
Mean difference (95% CI)	-14.6 (-18.2 to -10.9)		-11.1 (-14.83 to -7.4)	
<b>Change from baseline in fasting non-HDL (mg/dL)</b>	<b>N = 327</b>	<b>N = 324</b>	<b>N = 333</b>	<b>N = 315</b>
Baseline mean	113.4	114.6	115.2	114.9
Mean change (SD)	-0.5 (25.6)	17.6 (30.3)	-2.1 (25.3)	14.9 (28.1)
Mean Difference (95% CI)	-18.4 (-22.5 to -14.3)		-17.0 (-21.0 to -13.0)	
<b>Change from baseline in fasting cholesterol (mg/dL)</b>	<b>N = 327</b>	<b>N = 324</b>	<b>N = 333</b>	<b>N = 315</b>
Baseline mean	156.9	157.9	157.4	156.3
Mean change (SD)	4.0 (27.7)	21.9 (32.9)	-0.0 (27.5)	23.4 (29.1)
Mean difference (95% CI)	-18.1 (-22.5 to -13.6)		-23.1 (-27.3 to -19.0)	
<b>Change from baseline in fasting triglycerides (mg/dL)</b>	<b>N = 327</b>	<b>N = 324</b>	<b>N = 333</b>	<b>N = 315</b>
Baseline mean	110.9	117.2	119.5	123.2
Mean change (SD)	-1.1 (71.0)	22.5 (81.4)	-9.6 (72.8)	18.8 (90.3)
Mean difference (95% CI)	-25.7 (-36.6 to -14.7)		-30.1 (-41.3 to -19.0)	
<b>Change from baseline in fasting HDL cholesterol (mg/dL)</b>	<b>N = 327</b>	<b>N = 324</b>	<b>N = 333</b>	<b>N = 315</b>
Baseline mean	43.5	43.3	42.2	41.4
Mean change (SD)	4.5 (11.3)	4.2 (11.5)	2.0 (11.0)	8.4 (11.3)
Mean Difference, 95% CI	0.4 (-1.3 to 2.0)		-6.2 (-7.9 to -4.5)	

3TC = lamivudine; ABC = abacavir; AE = adverse event; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; NPS = not pre-specified; NR = not reported; SAE = serious adverse event; SD = standard deviation; TDF = tenofovir disoproxil fumarate.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

### Neuropsychiatric Adverse Events

Neuropsychiatric AEs at week 48 were considered a primary safety outcome in DRIVE-AHEAD, and three categories were specifically analyzed in a pre-specified order of statistical hierarchy: dizziness, sleep disorders and disturbances, and altered sensorium. A statistically significantly lower proportion of patients in the DOR arm reported all three AEs compared with those in the EFV arm; between-treatment differences were -28.3 (95% CI, -34.0 to -22.5), -13.5 (95% CI, -19.1 to -7.9), and -3.8 (95% CI, -7.6 to -0.3) for dizziness, sleep disorders and disturbances, and altered sensorium, respectively. Two additional categories of neuropsychiatric AEs, depression and suicide/self-injury and psychosis and psychotic disorders, occurred at a numerically lower proportion in the DOR arm than in the EFV arm (Table 26).

Data from 96 weeks showed a similar pattern for DRIVE-AHEAD patients, all five categories of neuropsychiatric AEs occurred at a lower frequency in the DOR arm compared with the EFV arm. The differences were most prominent for dizziness (10.2% versus 38.2%), sleep disorders and disturbances (14.0% versus 27.5%), and altered sensorium (5.2% versus 7.4%). Psychiatric disorders also occurred at a lower frequency in the DOR arm compared

with the EFV arm (21.7% versus 37.4%) In DRIVE-FORWARD, the proportions of patients experiencing neuropsychiatric AEs and psychiatric disorders were largely similar between the groups.

Among treatment-switch patients, the overall rate of neuropsychiatric events was low. However, a greater proportion of patients in the ISG arm reported dizziness and sleep disorders compared with the DSG arm, both at week 24 prior to the switch to DOR and week 48 after the switch. Psychiatric disorders were also seen at a greater frequency in the ISG arm at both time points.

**Table 26: Neuropsychiatric Adverse Events in Treatment-Naive Patients (48 Weeks)**

AEs	DRIVE-AHEAD			
	DOR/3TC/TDF N = 364	EFV/FTC/TDF N = 364	Treatment difference % (95% CI)	P value
Neuropsychiatric AEs	86 (23.6)	207 (56.9)		NPS
Dizziness	32 (8.8)	135 (37.1)	-28.3 (-34.0 to -22.5)	< 0.001
Sleep disorders and Disturbances	44 (12.1)	93 (25.5)	-13.5 (-19.1 to -7.9)	< 0.001
Altered sensorium	16 (4.4)	30 (8.2)	-3.8 (-7.6 to -0.3)	0.033
Depression and suicide/self-injury	15 (4.1)	24 (6.6)		NPS
Psychosis and psychotic disorders	1 (0.3)	4 (1.1)		NPS

3TC = lamivudine; AE = adverse event; CI = confidence interval; DOR = doravirine; EFV = efavirenz; FTC = emtricitabine; NPS = not pre-specified; TDF = tenofovir disoproxil fumarate.

Source: DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

### *Altered Hepatic Enzymes*

Measurements of hepatic enzymes showed an irregular pattern, depending on the grade of severity, treatment group, and trial. No one enzyme or severity grade was found to be consistently increased or decreased between-treatment arms across trials. Notably, the incidence of drug-induced liver injury, defined as having alanine transaminase or aspartate transaminase  $\geq 3 \times$  upper limit of normal range (ULN) plus bilirubin  $\geq 2 \times$  ULN and alkaline phosphatase  $< 2 \times$  ULN, was low or lacking in all trials. Results are summarized in Table 22 and Table 23.

### *Cardiovascular Disease or Events*

The overall incidence of cardiovascular disease was low in all trials, at  $< 3\%$  in each treatment group (Table 22 and Table 23).

### *Renal and Bone-Related Toxicity*

The overall incidence of renal and urinary disorders was low in all trials, at  $< 5\%$  in each treatment group (Table 22 and Table 23).

### *Skin Disorders*

Data for skin and subcutaneous tissue disorders as an organ class are reported here, and summarized in Table 22 and Table 23. Additionally, all rash-related events were reported as a composite outcome, including rash, erythematous rash, follicular rash, genital rash, generalized rash, macular rash, maculopapular rash, papular rash, pruritic rash, pustular rash, vesicular rash, and viral rash.

Skin disorders and rash-related events occurred at a similar frequency between-treatment arms in DRIVE-FORWARD. In DRIVE-AHEAD, the frequency of skin disorders and rash-related events was noticeably lower among patients receiving DOR compared with those receiving EFV. In DRIVE-SHIFT, the overall incidence of skin disorders and rash-related events was low, with generally similar frequency between-treatment arms.

## Discussion

### Summary of Available Evidence

The evidence base for this review comprised two DB trials (DRIVE-FORWARD, DRIVE-AHEAD) conducted in treatment-naive patients and one OL trial (DRIVE-SHIFT) conducted in virologically suppressed treatment-switch patients. All three studies were randomized, active-controlled, noninferiority trials; with a base study period of 96 and 48 weeks for the DB and OL studies, respectively. Treatments administered in the DB studies were DOR or DRV/r, each given in combination with 3TC/TDF or ABC/TDF (DRIVE-FORWARD), and DOR/3TC/TDF or EFV/FTC/TDF (DRIVE-AHEAD). In DRIVE-SHIFT, patients either immediately switched to DOR/3TC/TDF to be received for 48 weeks (immediate switch) or continued their baseline regimen (ritonavir or cobicistat-boosted PI, or an InSTI, or an NNRTI, each administered with two NRTIs) for 24 weeks before switching to DOR/3TC/TDF (delayed switch). The primary outcome in all trials was virologic suppression defined as the proportion of patients with HIV-1 RNA < 50 copies/mL (calculated using the FDA snapshot algorithm). In DRIVE-FORWARD and DRIVE-AHEAD the between-treatment differences for the primary efficacy outcome were analyzed at week 48, while in DRIVE-SHIFT the primary analysis compared the proportion of patients achieving HIV-1 RNA < 50 copies/mL at 48 weeks for the ISG versus those achieving this outcome at 24 weeks while on baseline regimen (DSG). The NIM was 10% and 8% for the DB and OL trials, respectively. Notable safety end points included changes in lipid levels and neuropsychiatric AEs. It should be noted that in addition to limited evidence for switching to a DOR regimen (specifically DOR/3TC/TDF) for patients who are virologically suppressed there is no evidence for use of a DOR regimen in patients who have failed to achieve virologic suppression on ART.

### Interpretation of Results

#### Efficacy

Even though the comparators chosen in the treatment-naive trials, DRV/r and EFV, are available in Canada, they are not the preferred choice of drugs for treatment initiation according to the clinical expert consulted for this review. The DHHS guidelines<sup>4</sup> widely recognized for the management and treatment of HIV recommend the following treatment combinations in treatment-naive patients: BIC/TAF/FTC, DTG/ABC/3TC, DTG/TDF/FTC, raltegravir/TDF/FTC; with 3TC as an alternative to FTC and tenofovir used with consideration of bone and renal toxicities and lipid levels.<sup>4</sup> The clinical expert agreed that the aforementioned regimens, in addition to FTC/EVG/cobicistat/TAF (Genvoya), are the most relevant comparators from a Canadian perspective. Notably, the DHHS guidelines recommend DOR/TDF/3TC and DOR plus TAF/FTC as initial regimens in certain clinical situations, including patients with a high cardiac risk and hyperlipidemia.<sup>4</sup>

For treatment-experienced patients with viral suppression, the DHHS guidelines do not provide a list of recommended therapies. Instead, selecting a new ART regimen should be based on patients' previous ART history, including virologic responses, past ART-associated toxicities and intolerances, resistance-test results, drug-drug interactions, and pill burden, in addition to other non-clinical considerations.<sup>4</sup> The baseline regimens for the treatment-switch patients in DRIVE-SHIFT, namely boosted PI, boosted EVG, and NNRTI, are relevant comparators in this setting.

The trials in treatment-naive patients (DRIVE-FORWARD and DRIVE-AHEAD) were conducted with sufficient methodological rigour, with appropriate statistical analyses plans, selection of trial population and outcomes, and adequate follow-up. A number of design features and methodological issues limited the validity and interpretability of the switch trial (DRIVE-SHIFT). The primary outcome for treatment-naive trials was consistent with the FDA snapshot algorithm for virologic suppression, i.e., HIV-1 RNA < 50 copies/mL at week 48. However, the switch trial also used the above end point as the primary outcome, as opposed to the FDA-recommended outcome of virologic failure, i.e., HIV-1 RNA  $\geq$  50 copies/mL at week 48.<sup>34</sup> Although the proportional difference in HIV-1 RNA  $\geq$  50 copies/mL between the treatment arms was compared statistically, adjustment for multiple comparisons was not made. The reported result for the primary efficacy outcome showed the 8% NIM was met. However, the FDA snapshot algorithm to account for missing data (missing data = failure) was not followed properly. Instead, some patients with missing data at week 48 had their blood samples reanalyzed from other sources and the data were added to the analyses dataset post hoc. Following this modification, the NIM was met for the primary efficacy outcome. However, noninferiority was not demonstrated with the true snapshot approach. Finally, testing of primary and secondary end points in the statistical hierarchy was based on different periods of exposure for the two treatment arms. Patients in the ISG arm received DOR/3TC/TDF for 48 weeks whereas those in the DSG arm received their baseline regimens for weeks 0 to 24 and DOR/3TC/TDF for weeks 24 to 48. Statistical comparisons were not made between the treatment arms at week 24 for most end points (including the primary efficacy end point), or were not controlled for multiplicity. Instead, results for the ISG arm at week 48 were compared with the DSG arm at week 24.

All trials met the a priori defined NIM (10% for treatment-naive and 8% for treatment-switch trials) for the primary efficacy outcome, i.e., virologic success. The virologic success rates across trials were approximately 80% in treatment-naive patients and > 90% in treatment-switch patients by week 48. The higher response rate among treatment-switch patients was expected because they achieved virologic suppression on a stable baseline regimen of ART at baseline. Among treatment-naive patients, the rate of discontinuation ranged between 13% and 19% at week 48, and between 18% and 29% at week 96 across trials. The primary causes for study discontinuation were AEs, lack of efficacy, lost to follow-up, and patient withdrawal. Two reasons were provided by the manufacturer to explain the increased dropout rates and the subsequent decreased virologic success rate, in particular from week 48 to week 96. First, the pill burden in the trials was high (e.g., four pills/day in DRIVE-FORWARD). Second, patients who met the stringent PDVF criteria had to discontinue the study. Under this rule, patients who experienced a viral rebound (i.e., confirmed HIV-1 RNA  $\geq$  50 copies/mL after having been suppressed to < 50 copies/mL) during the study were required to discontinue. Other recent clinical trials used a higher threshold for PDVF: 200 to 400 copies/mL HIV-1 RNA. Additionally, the majority of the patients who met the PDVF criteria had < 200 copies/mL HIV RNA between the viral failure visit and the viral failure confirmation visit. It is possible that several patients could have been re-suppressed to < 50 copies/mL had they been allowed to continue in the trial. Results using the OF

approach, which excluded patients who discontinued for non-efficacy-related reasons and therefore can be considered more reflective of viral efficacy, confirmed the findings and showed a higher response rate in both arms within the trials.

Despite the relatively lower virologic success rates among treatment-naive patients overall, patients receiving DOR in both trials had a numerically greater success rate at both time points. Likewise, a smaller proportion of patients receiving DOR had no virologic data available. These differences can partially be attributed to the lower discontinuation rate among the DOR recipients, resulting from lost to follow-up, non-compliance with study drug, and withdrawal by patient, as described above.

Notably, the proportions of patients with HIV-1 RNA  $\geq$  50 copies/mL were higher than expected according to the clinical expert, ranging between 10% and 14% at week 48, and between 12% and 21% at week 96. Between-treatment differences were largely similar. It is unclear if all of the patients were classified appropriately according to the FDA snapshot algorithm for the included studies, as patients lacking virologic data were not included as failures (assumption of HIV-1 RNA  $\geq$  50 copies/mL). The impact this would have had on the results is uncertain.

Among other efficacy end points, resistance to the study medications, i.e., background NRTI or the third ARV agent, occurred infrequently. Adherence to treatment was generally high, with most patients (> 85%) reporting an adherence of 90% or more. However, overall adherence among all participants was likely much lower owing to the discontinuation rate, which occurred in part due to high pill burden. Results from the subgroup analyses indicated that the virologic success rate was lower in patients with baseline plasma HIV-1 RNA > 100,000 copies/mL. Patients consulted for this review indicated that the stigma and stress associated with HIV are important outcomes for them, yet none of the trials assessed such outcomes. One HRQoL measure, EQ-5D-5L, was assessed in DRIVE-SHIFT. However, only the self-reported VAS component was reported, and no index score was generated which includes a domain assessing anxiety.

## Harms

The overall frequency of AEs among treatment-naive patients increased only slightly between week 48 and week 96 (overall incidence 78% to 91% at week 48 and 82% to 94% at week 96). Treatment-naive patients experienced more AEs (range 78% to 91%, data not presented) than treatment-switch patients (range 52% to 81%) by week 48. Patients in the ISG arm of DRIVE-SHIFT had an increased rate of AEs at week 24 compared with the baseline regimen at week 24 for the DSG arm; a pattern consistent with the notion that patients switching therapies are likely to experience more AEs versus those remaining on their baseline therapy. Common AEs across trials included diarrhea, headache, URTI, nausea, nasopharyngitis, pharyngitis, fatigue, back pain, bronchitis, cough, syphilis, upper abdominal pain, insomnia, dizziness, somnolence, abnormal dreams, and rash-related events. The frequency of SAEs was generally low among treatment-naive patients (5% to 9%), and even lower among treatment-switch patients (1% to 5%). Likewise, the frequency of WDAEs was low (1% to 8%), with a lower rate reported for treatment-switch patients. A total of 13 deaths was reported across the trials, of which one incidence in DRIVE-SHIFT was considered to be related to the study drug (primary cause of death: myocardial infarction), although no confirmatory diagnosis (diagnosis by a medical professional or autopsy) was done.

DOR showed an improvement in lipid profile compared with DRV/r and EFV (among treatment-naive patients) and ritonavir or cobicistat-boosted PI, cobicistat-boosted InSTI, or NNRTI (among switch patients) at all time points. DOR was also associated with a lower incidence of neuropsychiatric AEs. However, the benefits were largely in comparison with EFV, which is commonly associated with neuropsychiatric side effects. The effects of DOR on hepatic enzymes, cardiovascular disease, renal and bone-related toxicity, and skin disorders are less clear.

### Indirect Comparisons

The manufacturer-submitted network meta-analysis (NMA)<sup>35</sup> suggests that, with respect to virologic success (HIV-1 RNA < 50 copies/mL) [REDACTED]

[REDACTED]

[REDACTED] The NMA did not provide adequate information on the statistical analyses plan to assess the validity of the results and NMA assumptions. The missing information, coupled with the small network size, and the lack of assessing NMA assumptions, and the differences in trial design and the definition used for PDVF to determine virologic response, translate to a high degree of uncertainty in the presented efficacy and safety results. Other limitations include the limited scope of the manufacturer-submitted indirect comparison (IDC), in which only interventions that are relevant to the economic model in treatment-naive patients were analyzed, without assessing relevant comparators such as [REDACTED]

[REDACTED]

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

As an NNRTI, DOR has some positive attributes compared with its predecessors in the class, including the lack of neuropsychiatric side effects (compared with EFV), lack of requirement to be taken with food and with normal gastric acidity (unlike rilpivirine) and once-daily dosing (unlike etravirine).

Its role will be limited by its late entry into the market. As a single daily-dose “third component” of an antiretroviral combination, it has been preceded to market by rilpivirine, DTG, and boosted DRV, among others. As a co-formulated STR, Delstrigo (DOR/3TC/TDF) is one of almost a dozen available single-tablet options, including Atripla (and generics), Complera, Odefsey, Stribild, Genvoya, Triumeq, Biktarvy, Symtuza and Juluca.

The most commonly prescribed antivirals for treatment-naive patients, or those switching for reasons of convenience or tolerance, are the STRs, in particular Genvoya and Triumeq. Although they come with their own idiosyncracies, most are well tolerated, convenient, and effective. Use of the DOR STR would be infrequent, as the tenofovir component of this Delstrigo STR is the TDF formulation, which is associated with renal and bone toxicities. The newer TAF, found in Biktarvy and Genvoya, is not associated with these side effects and is generally preferred by prescribing physicians.

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



As a single component of a regimen, DOR (Pifeltro) would be a reasonable treatment consideration if an STR is not available or an option for the individual patient. Most likely, it would be used where a tenofovir-containing regimen is not considered ideal, and where side effects of Triumeq have occurred. It would most likely be used with Kivexa (or its generic counterpart). Its use is anticipated to be infrequent.

## Conclusions

Results from two DB RCTs in treatment-naive patients demonstrate that DOR is noninferior to DRV/r when given in combination with FTC/TDF or ABC/3TC, and that DOR/3TC/TDF is noninferior to EFV/FTC/TDF in achieving virologic suppression (HIV-1 RNA < 50 copies/mL) at week 48. Differential study discontinuation in both trials may have biased the estimates of comparative efficacy toward DOR and DOR/3TC/TDF, but the impact is unlikely to change the conclusion of noninferiority. DOR and DOR/3TC/TDF resulted in a more favourable lipid profile (LDL and non-HDL) compared with DRV/r and EFV/FTC/TDF, respectively, and DOR/3TC/TDF was associated with fewer neuropsychiatric events compared with EFV/FTC/TDF, a combination known for its neuropsychiatric effects due to its EFV component. The manufacturer-submitted IDC of ARVs in [REDACTED] did not include a number of relevant comparators (such as [REDACTED]). Further, the IDC suffered from methodologic limitations that resulted in a high degree of uncertainty in the estimates of comparative efficacy and safety between [REDACTED].

Results from one OL RCT in virologically suppressed, treatment-experienced patients suggest that DOR/3TC/TDF is noninferior to continuing baseline treatment (consisting of a ritonavir- or cobicistat-boosted PI, cobicistat-boosted InSTI, or NNRTI, each administered with two NRTIs) based on the primary outcome of HIV-1 RNA < 50 copies/mL. However, this finding is of questionable validity given the fact that the two treatment arms had an unequal period of exposure to the respective study drugs. Additionally, the FDA-recommended end point of interest for switch trials (HIV-1 RNA  $\geq$  50 copies/mL) was not included in the statistical hierarchy. Results for secondary outcomes included in the statistical hierarchy (LDL and non-HDL) provide support for a favourable impact of DOR/3TC/TDF on patients' lipid profiles.

## 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

One patient group, the Canadian Treatment Action Council (CTAC), provided input for this drug review. CTAC is a national non-governmental organization that focuses on access to treatment, care, and support for people living with HIV and hepatitis C. CTAC's organizational goals are to engage 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: a) individual people living with HIV (including hepatitis C co-infection); b) organizations, groups or projects with a substantial HIV mandate (including hepatitis C co-infection). Associate CTAC membership is open to any individual, organization, group, or project that supports CTAC's mandate and objective.

In the last two years CTAC has received funding in excess of \$50,000 from ViiV Healthcare. CTAC did not receive help from outside the organization to prepare this submission, or to collect and analyze data used in this submission.

### 2. Condition-Related Information

Data for this submission were obtained from seven patients with HIV (five men and two women) who attended a patient input consultation workshop in Toronto, Canada. The participants were in their 20s, 40s, or 50s, and had been receiving treatment for HIV for five to 34 years. In addition, survey data collected for a patient submission on dolutegravir was used to inform this patient submission.

HIV is a serious, life-threatening illness that threatens the immune system. Over time, if left untreated, HIV can compromise a person's immune system to the point that the body may no longer be able to fight off opportunistic infections. Access to, administration of, and adherence to highly active antiretroviral treatment can control progression of HIV such that patients generally manage their condition as a chronic illness. However, patients with HIV are more susceptible to inflammation and non-infectious comorbidities, including bone fractures, renal failure, and liver and cardiovascular disease. Many of those living with HIV experience negative mental health outcomes, whether as a side effect from treatment, or from facing stigma, discrimination, and related stress. Stigma is one of the more prominent issues dealt with, as explained by one respondent, "I still cannot come to terms with the fact that I'm HIV-positive, and I've been positive for 25 years. I still run away from it, and I have a hard time talking about it...." This is further highlighted by another respondent from the dolutegravir (DTG) rilpivirine survey regarding their interaction with 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 (from the DTG rilpivirine survey) 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."

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. Limited funding or services for addictions, mental health, housing, and food security can affect patients' HIV treatment. One respondent from the DTG consultations noted that difficulties understanding stigma and its impact, and navigating HIV-specific social services and institutional systems, including disability insurance and mortgages, have presented specific challenges. One respondent stated, "I am worried about the fact that HIV is now viewed as chronic, manageable disease. I still have good and bad days but, if HIV is now seen as something other than a disability, will I be forced to go back to work, even when I'm not well?"

Respondents all noted substantial impact on caregivers looking after patients living with HIV. One respondent highlighted that the challenges his/her 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 ability to acquire a social safety net" (from the DTG survey).

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

Data for this submission were obtained from seven patients with HIV who were receiving treatment for the past five to 34 years. These patients had been on their current therapy for five to 10 years with minor changes to therapy that were made due to other health problems or resistance that developed.

As a result of being on HIV treatment, many participants described noticeable improvements in their quality of life and ability to engage in daily activities. Discussing the overall impact of treatment on his life, one participant stated, "Not only do I feel healthy, I know I am thanks to the HIV medication. Without it, I would be dead by now." When asked whether treatment had improved their quality of life another respondent answered, "In 1995, the doctors said I had 2 months to live, and that I'd better get my affairs in order. I never expected that I'd still be alive." Another participant noted that, "My quality of life has improved. I'm now on a combination of drugs that has gotten me to an undetectable viral load."

Respondents to the dolutegravir survey also indicated that their treatment was effective at suppressing their viral load; but some had experienced severe adverse effects to older treatments such as zidovudine.

The CTAC stated that the increased risk of experiencing comorbidities associated with HIV may be due in part to antiretroviral treatments themselves. In addition, not all patients with HIV are able to achieve viral suppression despite trying multiple treatment regimens. Further, treatment adherence is necessary for therapy to be effective and to minimize the development of drug class resistance that would necessitate a change in therapy. CTAC stated that having the maximum possible treatment options is of clinical importance.

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

None of the patients surveyed had experience with doravirine. However, many expressed an interest in a drug with a new chemical composition that may provide another treatment option if resistance to other treatments is a problem. Differences in drug-drug interactions or adverse events noted for doravirine compared with some other treatments were considered important to the patients surveyed.

One participant noted that, "I like the fact that this medication has a new chemical composition. I like knowing the option is out there, since I am resistant to many, many of the current HIV drugs out there. My doctor told me, 'The meds that you are on now are the last ones available that you can take.'" Another participant from the DTG rilpivirine survey noted that, "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 regime for quite some time."

## Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–) Embase (1974–) <b>Note:</b> Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	December 12, 2018
Alerts:	Weekly search updates until project completion
Study types:	No search filters were applied
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
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
.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
.rn	Registry number
.nm	Name of substance word
.dq	Candidate Term Word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oomezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(pifeltro* or doravirine* or delstrigo* or MK-1439* or MK1439* or 913P6LK81M).ti,ab,ot,kf,hw,rn,nm.
2	1 use medall
3	*doravirine/ or (pifeltro* or doravirine* or delstrigo* or MK-1439* or MK1439*).ti,ab,kw,dq.
4	3 use oomezd
5	4 not (conference review or conference abstract).pt.
6	2 or 5
7	remove duplicates from 6

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search terms: pifeltro, doravirine, delstrigo, MK-1439, MK1439]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms: pifeltro, doravirine, delstrigo, MK-1439, MK1439]

## OTHER DATABASES

PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
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## Grey Literature

Dates for Search:	December 2018
Keywords:	Pifeltro (doravirine), HIV-1
Limits:	none

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:

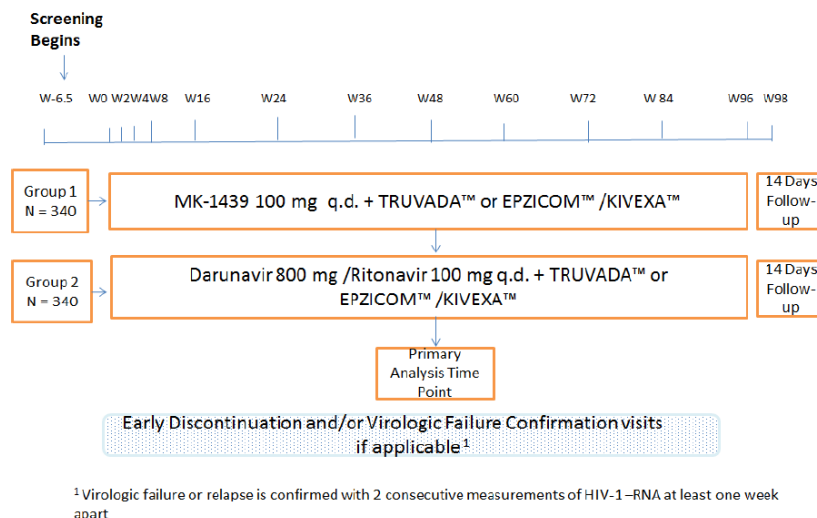
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Internet Search

## **Appendix 3: Excluded Studies**

None of the published studies identified in the initial literature and screened for full-text review were excluded.

## Appendix 4: Detailed Outcome Data

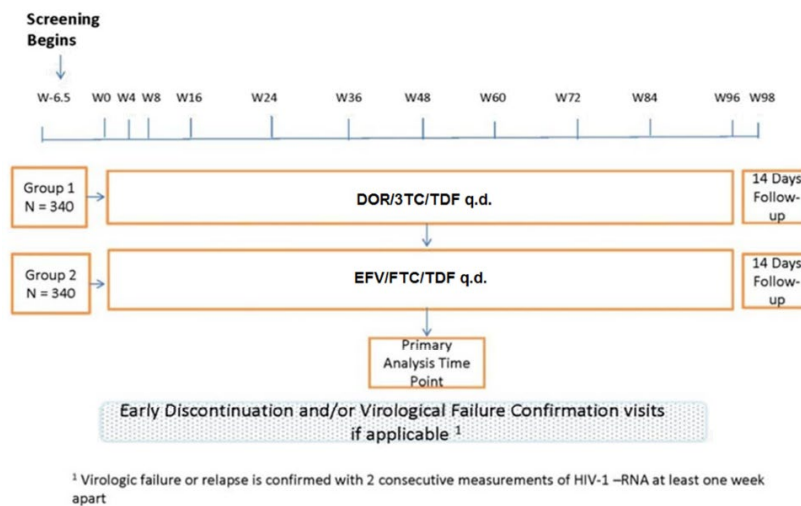
Figure 2: Trial Design for DRIVE-FORWARD Study



q.d. = once daily.

Source: DRIVE-FORWARD Clinical Study Report.<sup>5,6</sup>

Figure 3: Trial Design for DRIVE-AHEAD Study

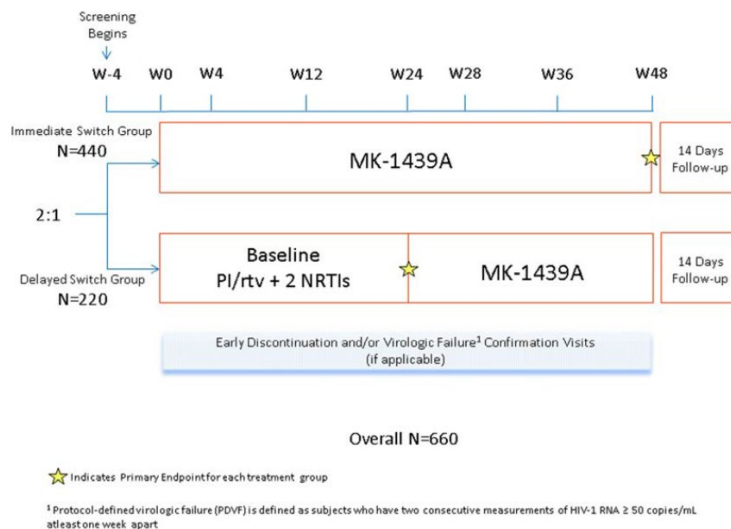


3TC = lamivudine; DOR = doravirine; EFV = efavirenz; FTC = emtricitabine; q.d. = once daily; TDF = tenofovir disoproxil fumarate.

Source: DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>



Figure 4: Trial Design for DRIVE-SHIFT Study



NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; rtv = ritonavir.

Source: DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

Table 27: Efficacy Outcomes – Treatment-Naive Patients (Sensitivity 48 Weeks)

Sensitivity analysis	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR N = 364	DRV/r N = 355	DOR/3TC/TDF N = 346	EFV/FTC/TDF N = 331
<b>Observed failure approach</b>				
Proportion of patients with HIV 1 RNA < 50 copies/mL <sup>a</sup>				
n (%)	321 (88.2)	306 (86.2)	307 (88.7)	294 (88.8)
Treatment difference % (95% CI)	1.9 (-3.1 to 6.8)		-0.2 (-4.9 to 4.6)	
<b>Per-protocol analysis</b>				
Proportion of patients with HIV 1 RNA < 50 copies/mL <sup>b</sup>				
n (%)	316 (89.5)	298 (87.4)	302 (89.3)	291 (85.8)
Treatment difference % (95% CI)	2.1 (-2.7 to 6.9)		3.6 (-1.3 to 8.5)	

3TC = lamivudine; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate.

<sup>a</sup> Observed failure approach.

<sup>b</sup> Per-protocol analysis (snapshot approach used for HIV-1 RNA < 50 copies/mL).

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

**Table 28: Efficacy Outcomes – Treatment-Experienced Patients (Sensitivity 48 Weeks)**

	DRIVE-SHIFT			
	ISG week 0-48 N = 413	DSG week 0-24 N = 215	ISG week 0-24 N = 427	DSG week 0-24 N = 215
<b>Observed failure approach</b>				
Proportion of patients with HIV-1 RNA < 50 copies/mL <sup>a</sup>				
n (%)	406 (98.3)	211 (98.1)	419 (98.1)	211 (98.1)
Treatment difference % (95% CI)	0.2 (-2.2 to 2.5)		-0.0 (-2.4 to 2.4)	
<b>Based on initial database lock<sup>b</sup></b>	N = 447	N = 223		
Proportion of patients with HIV-1 RNA < 50 copies/mL <sup>a</sup>				
n (%)	404 (90.4)	211 (94.6)	NR	NR
Treatment difference % (95% CI)	-4.2 (-8.4 to -0.1) NI not met			

CI = confidence interval; ISG = immediate switch group; DSG = delayed switch group; NI = noninferiority; NR = not reported; RNA = ribonucleic acid.

<sup>a</sup> Observed failure approach.

<sup>b</sup> Two patients in the ISG had missing HIV-1 RNA samples at week 48 based on the initial database lock and thus were counted as treatment failures.

Source: DRIVE-SHIFT Clinical Study Report.<sup>9</sup>

**Table 29: Efficacy Outcomes – Treatment-Naive Patients (Sensitivity 96 Weeks)**

Sensitivity analysis	DRIVE-FORWARD		DRIVE-AHEAD	
	DOR N = 342	DRV/r N = 323	DOR/3TC/TDF N = 337	EFV/FTC/TDF N = 312
<b>Observed failure approach</b>				
Proportion of patients with HIV 1 RNA < 50 copies/mL <sup>a</sup>				
n (%)	277 (81.0)	248 (76.8)	282 (83.7)	268 (85.9)
Treatment difference % (95% CI)	4.0 (-2.2 to 10.2)		-2.2 (-7.7 to 3.3)	
<b>Includes missing data due to Abbott recall</b>				
Proportion of patients with HIV 1 RNA < 50 copies/mL <sup>b</sup>				
n/N (%)	277/383 (72.3)	248/383 (64.8)	NA	NA
Treatment difference % (95% CI)	7.5 (0.9 to 14.1)			

3TC = lamivudine; CI = confidence interval; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; RNA = ribonucleic acid; TDF = tenofovir disoproxil fumarate.

<sup>a</sup> Observed failure approach.

<sup>b</sup> Sensitivity analysis including subjects missing HIV-1 RNA due to Abbott reagent recall; however, the snapshot approach was used to account for missing data.

Sources: DRIVE-FORWARD Clinical Study Report,<sup>5,6</sup> DRIVE-AHEAD Clinical Study Report.<sup>7,8</sup>

## Appendix 5: Summary of Indirect Comparisons

### Introduction

The clinical trials included in the CDR systematic review do not provide evidence of the comparative efficacy and safety of DOR relative to a number of relevant comparators. The objective of this Appendix is to summarize and critically appraise the evidence available regarding the comparative efficacy and safety of DOR 100 mg versus other treatments based on indirect comparisons (IDCs). Following is a summary and critical appraisal of the methods and main findings of the manufacturer-provided IDC.

### Methods

The manufacturer submitted one IDC which was reviewed, summarized, and critically appraised.<sup>35</sup> The CADTH Common Drug Review (CDR) team conducted an independent literature search for published IDCs that compared DOR with other relevant comparators; no additional publications were identified.

### Description of IDCs identified

[Redacted text]

[Redacted text]

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[Redacted]	[Redacted]
[Redacted]	[Redacted]
[Redacted]	[Redacted]
[Redacted]	[Redacted]

[Redacted text]

Review and Appraisal of Indirect Comparisons

Review of the Manufacturer-Sponsored Indirect Comparisons

*Objectives and Rationale for the Manufacturer-Sponsored Indirect Comparison*

[Redacted text block]

Methods for Indirect Comparison

*Study Eligibility and Selection Process*

**Systematic Review**

[Redacted text block]

[Redacted text block]

*Data Extraction*

[Redacted text block]

*Comparators*

- [Redacted list item]

*Outcomes*

[Redacted text block]

*Quality Assessment of Included Studies*

[Redacted text block]

*Evidence Network*

[Redacted text block]

*Indirect Comparison Methods*

[Redacted text block]

**Results**

**Baseline Characteristics**

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**Efficacy and Safety**

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[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[Redacted]

### Critical Appraisal

[Redacted]

The main limitation of the manufacturer-submitted IDC is the large extent of missing information pertaining to the methods used for conducting the network meta-analysis (NMA) and assessing the validity of the results, as described in the IDC methods previously. The missing information hinders our ability to assess the level of certainty in the presented results. The NMA report did not provide adequate information on the statistical analyses methods. Additionally, subgroup analysis by important patient baseline characteristics, disease severity (HIV ribonucleic acid level) was not reported. Therefore, there is significant uncertainty regarding the methodological rigour of the NMA, validity of the statistical analyses plan, and core assumptions of a NMA (transitivity, heterogeneity, and consistency). CDR requested these details from the manufacturer, but they were not provided or lacked adequate information.

[Redacted]

[REDACTED]

[REDACTED]

In terms of the results, the clinical relevance of the findings is unclear, considering the lack of many essential items to allow CDR to better assess the level of uncertainty in the presented results. Furthermore, many of the connections in the networks were only informed by a single trial, which increases the uncertainty in the analysis. These findings therefore cannot be considered strong evidence in support of doravirine providing greater clinical benefits and safety compared with the aforementioned comparators. Overall, the NMA used a limited set of comparators to ensure a connected network. However, this excluded a number of relevant comparators, including [REDACTED]

[REDACTED]. An important limitation of the overall body of evidence was that the scope of this NMA did not include [REDACTED].

### Conclusion

The manufacturer-submitted NMA suggests that, with respect to virologic success (HIV-1 RNA < 50 copies/mL) [REDACTED]

[REDACTED]

[REDACTED] The NMA did not provide adequate information on the statistical analyses plan to assess the validity of the results or the NMA assumptions. The missing information, coupled with the small network size, and the lack of assessment of NMA assumptions, and the differences in trial design and the definition used for PDVF to determine virologic response, translate to a high degree of uncertainty in the presented efficacy and safety results. Other limitations include the limited scope of the manufacturer-submitted IDC, in which only interventions that are relevant to the economic model in treatment-naive patients were analyzed, without assessing relevant comparators such as [REDACTED]

[REDACTED]

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