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CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

**DORAVIRINE/LAMIVUDINE/TENOFOVIR DISOPROXIL FUMARATE (Delstrigo — Merck Canada Inc.)**
Indication: As a complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to doravirine (DOR), lamivudine (3TC), or tenofovir.

**RECOMMENDATION**
The CADTH Canadian Drug Expert Committee (CDEC) recommends that DOR/3TC/tenofovir disoproxil fumarate (TDF) be reimbursed as a complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to DOR, 3TC, or tenofovir only if the following condition is met.

**Condition for Reimbursement**

**Pricing Condition**
1. The total cost of treatment with DOR/3TC/TDF should not exceed the total drug plan cost of treatment with the least costly alternative regimen for the treatment of HIV-1.


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| Service Line: | CADTH Drug Reimbursement Recommendation |
| Version: | Final |
| Publication Date: | May 16, 2019 |
| Report Length: | 7 Pages |

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

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## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that DOR/3TC/tenofovir disoproxil fumarate (TDF) be reimbursed as a complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to DOR, 3TC, or tenofovir only if the following condition is met.

## Condition for Reimbursement

**Pricing Condition**

1. The total cost of treatment with DOR/3TC/TDF should not exceed the total drug plan cost of treatment with the least costly alternative regimen for the treatment of HIV-1.

## Reasons for the Recommendation

1. In one double-blind randomized controlled trial conducted in treatment-naive patients with HIV-1 (DRIVE-AHEAD, N = 728), with a primary outcome of the proportion of patients with HIV-1 RNA < 50 copies/mL at week 48, DOR/3TC/TDF was noninferior to efavirenz (EFV)/emtricitabine (FTC)/TDF.
2. At the manufacturer-submitted price of $28.79 per day, DOR/3TC/TDF is $17.46 more costly than the current list price of EFV/FTC/TDF which is the comparator in the pivotal trial in treatment-naive patients. Given the lack of evidence that DOR/3TC/TDF offers superior efficacy or safety compared with other currently used single tablet regimens (STRs), CDEC considered that a price premium over available STRs is not warranted.

## Implementation Considerations

- The committee noted that several jurisdictions have specific reimbursement criteria for drugs for the treatment of HIV-1 and that they may wish to reimburse DOR/3TC/TDF in a manner similar to other HIV-1 treatment regimens.

## Discussion Points

- CDEC discussed that there is no unmet need for another antiretroviral (ARV) regimen for the treatment of HIV-1 given the numerous single- and double-tablet regimens available, and that appropriate regimens to manage patient-specific needs (e.g., avoidance of drug-drug interactions or adverse events [AEs]) are easily identified, given the large number of available regimens. CDEC noted that the US Department of Health and Human Services does not recommend DOR/3TC/TDF as initial therapy except in certain clinical situations. The committee discussed that tenofovir alafenamide fumarate (TAF)-containing STRs are likely to be chosen over DOR/3TC/TDF, given the potential for renal and bone toxicities with TDF.
- CDEC discussed that DOR/3TC/TDF was demonstrated to be noninferior with respect to achieving virologic success and suggested a more favourable safety profile with respect to neuropsychiatric AEs and lipid profile versus EFV/FTC/TDF in DRIVE-AHEAD. However, it was noted that EFV/FTC/TDF is an older regimen that is not often used in current clinical practice, due to its unfavourable adverse event profile, particularly related to neuropsychiatric AEs. The comparative efficacy and safety of DOR/3TC/TDF versus more commonly used regimens for initial treatment is unknown.
- CDEC discussed that the DRIVE-SHIFT trial suggests that virologically suppressed patients on a stable ARV regimen who switch to DOR/3TC/TDF are able to maintain virologic suppression at 48 weeks. However, CDEC noted that DRIVE-SHIFT has a number of methodologic limitations. For that reason there is some uncertainty surrounding the comparative effectiveness of DOR/3TC/TDF in treatment experienced patients. In addition, none of the available trials provide evidence of the clinical benefit of DOR/3TC/TDF in patients who have failed prior antiretroviral therapy (ART).

## Background

DELSTRIGO is a fixed-dose combination product containing 100 mg of DOR, 300 mg of 3TC, and 300 mg of TDF. DOR is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1; 3TC and TDF are nucleoside reverse transcriptase inhibitors (NRTIs). DOR/3TC/TDF has a Health Canada indication as a complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to DOR, 3TC, or tenofovir. The recommended dosage regimen is one tablet taken orally once daily with or without food.

## Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the clinical evidence (efficacy and safety) of DOR/3TC/TDF, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with HIV, and patient group–submitted information about outcomes and issues important to patients.

### Summary of Patient Input

One patient group, the Canadian Treatment Action Council, provided input for this submission. Patient perspectives were obtained from a consultation workshop in Toronto and survey data collected for the patient submission for a different drug (dolutegravir). The following is a summary of key input from the perspective of the patient group:

- Patients are generally able to manage their symptoms and disease progression; however, they are more susceptible to inflammation and non-infectious comorbidities. Patients indicated that stigma, discrimination, and related stress are a major obstacle to their well-being.
- Patients' physical and mental state can often be exacerbated by various social determinants of health, including access to treatment, experience of health care professionals in treating patients with HIV, and availability of resources.
- Patients noted that that their treatments were generally effective at suppressing the viral load, and resulted in an improved quality of life and ability to engage in daily activities. Instances of treatment-associated side effects and failure to achieve viral suppression despite trying multiple treatments were noted. Thus, the patient input emphasized the importance of having the maximum possible treatment options available.
- The patient group was not able to consult with any patients on DOR, therefore no information was provided on expectations for DOR alone or as a combination therapy. However, patients noted that new medications with fewer side effects and different chemical composition would be beneficial; the latter would likely lower the risk of developing drug resistance and drug-drug interactions.

### Clinical Trials

The systematic review included two phase III active-controlled, non-inferiority trials: one double-blind trial (DRIVE-AHEAD, N = 728) conducted in treatment-naive patients and one open-label trial (DRIVE-SHIFT, N = 673) conducted in virologically suppressed patients on a stable ARV regimen. DRIVE-AHEAD and DRIVE-SHIFT had a total follow-up duration of 96 weeks and 48 weeks, respectively.

Patients in DRIVE-AHEAD received DOR/3TC/TDF 100 mg/300 mg/300 mg or EFV/FTC/TDF, 600 mg/200 mg/300 mg once daily. In DRIVE-SHIFT, patients either immediately switched to DOR/3TC/TDF for 48 weeks (immediate switch group [ISG]) or continued their baseline regimen for 24 weeks (consisting of a ritonavir- or cobicistat-boosted protease inhibitor [PI], or cobicistat-boosted integrase strand transfer inhibitor, or NNRTI, each administered with two NRTIs before switching to DOR/3TC/TDF [delayed-switch group] [DSG]). Overall discontinuations between treatment arms ranged from 18% to 24% in the DRIVE-AHEAD trial by week 96, and 8% to 10% in the DRIVE-SHIFT trial by week 48.

Limitations in DRIVE-AHEAD include the use of a comparator regimen that is not commonly prescribed in Canadian clinical practice due to the neuropsychiatric side effects associated with EFV, which may overstate the comparative safety of DOR. In addition, the higher discontinuation rate in the EFV arm compared with the DOR arms may overestimate the comparative efficacy of DOR, given that those who discontinued the study were considered not to have achieved the primary outcome. DRIVE-SHIFT had a number of limitations, including the primary efficacy end point not being consistent with the latest FDA recommendations, not following the FDA-recommended snapshot algorithm for addressing missing values specifically for the primary outcome, and an unequal follow-up duration between the treatment arms for the primary analyses.

## Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Virologic success: Proportion of patients with HIV-1 RNA < 50 copies/mL as determined by the US FDA-defined snapshot algorithm (primary outcome for all studies).
- Virologic failure: Proportion of patients with HIV-1 RNA ≥ 50 copies/mL as determined by the US FDA-defined snapshot algorithm.
- CD4 cell count.
- Adherence to medication.
- Resistance.
- Notable harms: lipid profile and neuropsychiatric AEs.

## Efficacy

### *Treatment-naive patients*

Among treatment-naive patients, the primary outcome (proportion of patients with HIV-1 RNA < 50 copies/mL at week 48) was achieved by 84.3% and 80.8% patients receiving DOR/3TC/TDF and EFV/FTC/TDF, respectively, with a between-treatment difference of 3.5% (95% confidence interval [CI], –2.0 to 9.0). Thus, the pre-specified non-inferiority margin of 10% was met, since the lower bound of the 95% CI for treatment difference was above −10 percentage points. Non-inferiority was confirmed in the per-protocol population and sensitivity analyses using the observed failure (missing = excluded) approach. The proportions of patients with virologic success at week 96 were 77.5% and 73.6% for patients receiving DOR/3TC/TDF and EFV/ FTC/TDF, respectively. The proportions of patients with HIV-1 RNA ≥ 50 copies/mL (virologic failure) at week 48 were similar between the treatment arms; 10.7% versus 10.2% for DOR/3TC/TDF and EFV/FTC/TDF, respectively. The proportions of patients with HIV-1 RNA ≥ 50 copies/mL at 96 weeks were 15.1% versus 12.1% for DOR/3TC/TDF and EFV/FTC/TDF, respectively.

The between-treatment differences in mean changes in CD4 cell count from baseline in DRIVE-AHEAD were 10.1 (95% CI, -16.1 to 36.3) at week 48, and 14.7 (95% CI, –18.7 to 48.2) at week 96.

Resistance to any of the study medications occurred very infrequently, < 15 cases in either treatment group. Among patients who completed each trial, adherence to treatment was generally high, with most patients (> 85%) reporting an adherence of 90% or more.

### *Treatment-switch/experienced patients*

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; 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 continuing treatment with baseline regimen. However, DRIVE-SHIFT had a number of methodologic 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; between-treatment comparisons based on the same duration of follow up would have more internally validity. 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). 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 non-inferiority margin 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.

The treatment differences in mean CD4 cell count changes from baseline at the primary (ISG 0-48 versus DSG 0-24 weeks) and secondary time points (ISG 0-24 versus DSG 0-24 weeks) were –4.0 (95% CI, –31.6 to 23.5) and –12.8 (95% CI, –41.1 to 15.4), respectively.

One incidence of resistance was reported by week 48. Adherence with the study medication regimen was ≥ 90% for most participants (> 90%) in the ISG and for the DSG arm before and after switching treatment.

## Harms (Safety)

### *Treatment-naive patients*

- Overall AEs were largely similar between treatment arms in in DRIVE-AHEAD (88.2% and 93.1% of patients in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively) at week 96. Serious AEs (SAEs) were also reported in a similar proportion between treatment arms: 5.8% and 8.2% in DRIVE-AHEAD.
- The proportion of patients who withdrew from the trials due to AEs (WDAEs) ranged between 3.0% and 7.4% in DRIVE-AHEAD.
- There were six deaths in total. None of the deaths were deemed related to treatment.
- An assessment of lipid profile showed an improvement with DOR/3TC/TDF compared with EFV/FTC/TDF, with statistically significant between-treatment differences in mean changes from baseline in fasting low density lipoprotein (LDL) of –10.01 (95% CI, –13.53 to –6.49) and in mean changes from baseline in fasting non-high density lipoprotein (HDL) of –17.02 (95% CI, –20.89 to –13.16) at week 48. These treatment differences were carried forward at week 96; however, these analyses were not controlled for multiplicity. Results for other lipid outcomes were not adjusted for multiplicity.
- A number of neuropsychiatric AEs were assessed; however, statistical comparisons with multiplicity adjustment were only done for the proportion of patients reporting three outcomes. Patients receiving DOR/3TC/TDF had statistically significantly less dizziness, sleep disorders and disturbances, and altered sensorium at week 48, 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.

### *Treatment-switch/experienced patients*

- Overall, 80.3% of the patients in the ISG arm experienced AEs at week 48. 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), 60.3% of patients in the DSG arm experienced AEs post treatment-switch. The number of patients experiencing SAEs and WDAEs did not exceed 5% in any arms at either time point.
- There were two deaths, both in the ISG arm, one of which was deemed to be related to treatment, although no confirmatory diagnosis was made.
- DOR/3TC/TDF showed an improvement in fasting LDL and non-HDL versus the comparator arm at week 24, with between-treatment differences of –15.29 (95% CI, –18.99 to –11.59) and –23.90 (95% CI, –28.14 to –19.65), respectively. These results as well as other lipid outcomes were not adjusted for multiplicity. Neuropsychiatric AEs were not analyzed statistically.

### Cost and Cost-Effectiveness

DOR/3TC/TDF is a once daily STR containing DOR 100 mg, 3TC 300 mg, and TDF 300 mg. The submitted price is $28.79 per tablet. The manufacturer submitted a cost comparison of DOR/3TC/TDF to the individual components DOR 100 mg plus 3TC 300 mg plus TDF 300 mg. The manufacturer reported that at the submitted price of $28.79, DOR/3TC/TDF is similar in price to the individual component medications, and less costly than most STRs.

CADTH identified the following limitations and considerations with the manufacturer's submission:

- Variations exist in publicly available prices across jurisdictions for the backbone medications 3TC and TDF such that DOR/3TC/TDF may lead to cost savings or incremental costs depending on the jurisdiction.
- A lower price of EFV/TDF/FTC was identified than the one considered by the manufacturer.
- Additional relevant STR comparators (i.e., Biktarvy, Juluca, and Symtuza) were not considered by the manufacturer.
- Compared with other STRs, DOR/3TC/TDF is between 17% and 45% less costly, with the exception of EFV/TDF/FTC. The daily cost of DOR/3TC/TDF is $17.46 greater (154%) than EFV/TDF/FTC.
- DOR/3TC/TDF contains an older preparation of tenofovir, which has greater risk of renal toxicity and bone mineral density loss compared with the newer preparation, tenofovir alafenamide.

## CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

## April 10, 2019 Meeting

## Regrets

Two CDEC members did not attend.

## Conflicts of Interest

None