CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Dolutegravir/Rilpivirine (Juluca — ViiV Healthcare)

Indication: the treatment of human immunodeficiency virus (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies per mL)

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dolutegravir/rilpivirine (DTG/RPV) be reimbursed as a complete regimen to replace the current antiretroviral (cARV) regimen for the treatment of human immunodeficiency virus (HIV-1) infection in adults who are virologically stable and suppressed (HIV-1 RNA less than 50 copies per mL), if the following criterion and condition are met:

Criterion

- Under the care of a practitioner experienced in the care of patients with HIV

Condition

- A reduced price

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Dolutegravir/Rilpivirine (Juluca — ViiV Healthcare)

Indication: HIV infection

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dolutegravir/rilpivirine (DTG/RPV) be reimbursed as a complete regimen to replace the current antiretroviral (cARV) regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically stable and suppressed (i.e., fewer than 50 copies per mL of HIV-1 ribonucleic acid [RNA]), if the following criterion and condition are met:

Criterion:

- Under the care of a practitioner experienced in the care of patients with HIV

Condition:

- A reduced price

Reasons for the Recommendation:

1. In two phase III, open-label, noninferiority randomized controlled trials (RCTs) (SWORD-1, n = 510; SWORD-2, n = 518), patients who were switched from a stable, virologically suppressive (fewer than 50 copies per mL of HIV-1 RNA) triple-ARV regimen to a dual-therapy antiretroviral (ARV) regimen of dolutegravir (DTG) 50 mg plus rilpivirine (RPV) 25 mg maintained similar rates of viral load suppression (approximately 95%) after 48 weeks of treatment as the patients who remained on a stable, virologically suppressive triple-therapy ARV regimen. Virologic failure rates at 48 weeks were low (≤ 2%) in both groups in both trials. There were no significant differences in safety between treatment groups in both trials.
2. Although the annual cost of DTG/RPV is lower than the annual cost of triple-ARV regimens, it is also associated with fewer quality-adjusted life-years (QALYs) and is therefore associated with a net loss in health outcomes over a lifetime horizon. Hence, there is uncertainty associated with the cost-effectiveness of DTG/RPV and it is therefore uncertain whether switching to dual therapy offers reasonable value at the submitted price. Furthermore, at the submitted price, the cost of the fixed-dose combination is more costly than the individual components.

Of Note:

The Committee noted there is no evidence to justify the cost of DTG/RPV ($34.87 daily) exceeding the cost of the individual components, DTG plus RPV ($34.39 daily).

Discussion Points:

- The Committee noted that although the cost of DTG/RPV appears to be less than the publicly available cost of other recommended or currently used triple-combination regimens, participating drug programs may have lower negotiated prices that should be considered when assessing the comparable cost savings of DTG/RPV.
- While the manufacturer suggested that DTG/RPV is associated with a loss of health (0.09 loss in QALYs), the Committee felt that, given the evidence from the SWORD trials, there is uncertainty regarding whether DTG/RPV would result in worse outcomes in practice and noted that there are patients who may benefit from treatment.
- The Committee discussed that the US Department of Health and Human Services (DHHS) guidelines recommend more intensive monitoring in the first three months following a regimen switch.

Background:

DTG/RPV has a Health Canada indication as a complete regimen to replace the cARV regimen for the treatment of HIV-1 in adults who are virologically stable and suppressed (HIV-1 RNA < 50 copies per mL). DTG is an integrase strand transfer inhibitor and RPV is a non-nucleoside reverse transcriptase inhibitor. DTG/RPV is available as a fixed-dose combination (50 mg/25 mg) and the Health Canada recommended dose is one tablet taken once daily with food to ensure optimal absorption of RPV.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of DTG 50 mg plus RPV 25 mg 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-1 infection, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information:

One patient group, the Canadian Treatment Action Council, provided input for this submission. Patient perspectives were obtained from a national consultation webinar and a survey, and from survey data used in patient submissions for other HIV treatments. The following is a summary of key input from the perspective of the patient group(s):

- HIV infection can lead to a life-threatening disease that predisposes patients to opportunistic infections if left untreated; however, administration of and adherence to highly active antiretroviral treatment can control the progression of HIV disease.
- In addition to both the mental and physical effects of HIV and its treatment, people with HIV continue to experience stigma, discrimination, and related stress.
- Although people with HIV can live long lives and manage their HIV infection as a chronic illness, they express concern around experience with effects characterized as "accelerated aging": greater susceptibility at an earlier age to inflammation and non-infectious comorbidities, including bone fractures and kidney, liver, and cardiovascular disease.
- Patients reported that their treatment was successful in suppressing viral load. However, the length of time on current therapy ranged from four months to eight years (for people living with HIV for between 5 and 34 years), implying there have been past changes in treatment approaches. (Since people have varying responses to treatments, including significant side effects, sometimes new treatment regimens have to be used when those in use become less effective or can no longer be tolerated.) Respondents noted the need for multiple treatment options to address the fact that patients have varying responses to different treatments.

Clinical Trials

The systematic review included two phase III switch trials (SWORD-1, N = 510; SWORD-2, N = 518). SWORD-1 and SWORD-2 were identical open-label, active-controlled, randomized (1:1) noninferiority trials that enrolled adults with HIV-1 who were virologically stable with a suppressed viral load (HIV-1 RNA < 50 copies per mL). Patients were randomly assigned to switch to a once-daily regimen of 50 mg DTG plus 25 mg RPV (administered as individual drugs) or to continue with their cARV regimen for 48 weeks. The remaining 52 to 148 weeks ("late-switch" phase) of both trials were non-comparative in design and constituted a long-term extension intended to support the findings from the early-switch phase. For each trial, similar proportions of patients in the DTG/RPV group (94%) compared with the cARV group (93%) completed the early-switch phase.

Outcomes

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

- virologic success — percentage of patients with HIV-RNA < 50 copies/mL (FDA-defined snapshot algorithm)
- virologic failure — percentage of patients with HIV-RNA ≥ 50 copies/mL (FDA-defined snapshot algorithm)
- change from baseline in CD4+ lymphocyte count

- health-related quality of life
- adherence to medication
- bone mineral density

The primary efficacy outcome for both SWORD trials was the proportion of patients with plasma HIV-1 RNA < 50 copies/mL at week 48.

Efficacy

- In SWORD-1 and SWORD-2, DTG plus RPV was noninferior to cARV with respect to the percentage of patients with HIV-RNA < 50 copies/mL. The differences in proportions were:
  - SWORD-1: −0.6% (95% confidence interval [CI], −4.3% to 3.0%) in the intention-to-treat-exposed (ITT-E) population
  - SWORD-2: 0.2% (95% CI, −3.9% to 4.2%) in the ITT-E population
  - pooled SWORD-1 and SWORD-2: −0.2% (95% CI, −3.0% to 2.5%) in the ITT-E population.

  In all three analyses, the above-the-noninferiority margin (NI) specified by the manufacturer (10% for individual trials and 8% for the pooled data) was met. Further, the secondary per-protocol (PP) analyses supported the primary analyses.
- In SWORD-1, a similar proportion of patients taking DTG plus RPV (< 1%) compared with cARV (< 1%) were classified as virologic failures at week 48 [difference: 0.0% (95% CI, −1.3% to 1.4%]. Likewise, in SWORD-2, less than 1% of patients taking DTG plus RPV compared with 2% cARV were classified as virologic failures at week 48 (difference: −1.0% [95% CI, −2.4% to 0.5%]). In the pooled analysis, less than 1% of patients taking DTG plus RPV compared with 1% of patients taking cARV were classified as virologic failures at week 48 (difference: −0.5% [95% CI, −1.4% to 0.5%]). In all analyses, the upper bound of the 95% CI was less than the 4% NI margin recommended by the FDA for switch trials.
- In both SWORD-1 and SWORD-2, median CD4+ count increased from baseline to week 48 with no notable between-treatment differences.
- There were no differences in health-related quality of life among patients receiving DTG plus RPV versus cARV.
- In both SWORD-1 and SWORD-2, the change in self-rated adherence from baseline to week 48 was negligible.
- Preliminary data for the ongoing late-switch phase (week 52 to week 148) were available as a limited data set covering up to week 100. At the end of 100 weeks, [redacted].

Harms (Safety and Tolerability)

- In both the SWORD-1 and SWORD-2 trials, there were similar rates of serious adverse events with DTG plus RPV compared with cARV groups (4% versus 5% in SWORD-1 and 7% versus 4% in SWORD-2, respectively).
- Overall adverse events were more frequent in the DTG plus RPV group compared with cARV for both SWORD-1 (79% versus 74%) and SWORD-2 (75% versus 68%).
- There was no indication of an adverse impact on renal function from short-term exposure (i.e., 48 weeks) to DTG plus RPV.
- Bone-related harms (changes in bone mineral density but not fracture incidence) were addressed in a substudy, which showed small increases in areal density of the hip and lumbar spine with DTG plus RPV compared with tenofovir disoproxil fumarate (TDF)-based cARV at week 48, with a between-group mean difference of 1.32% (95% CI, 0.07% to 2.57%; *P* = 0.039). The difference was not thought to be clinically meaningful.

Cost and Cost-Effectiveness

DTG/RPV (Juluca) is available as a fixed-dose combination (50 mg/25 mg) tablet and it is taken once daily. At a manufacturer-submitted unit price of $34.87 per tablet, the annual cost of DTG/RPV is approximately $12,728 per patient. The daily cost of the components of Juluca (DTG plus RPV: $34.39) is less than the DTG/RPV fixed-dose combination tablet. When compared with the least costly ARV regimen, according to the DHHS-recommended initial regimens (DTG plus emtricitabine/tenofovir alafenamide (FTC/TAF): $14,454 per patient per year), DTG/RPV results in savings of approximately $1,726 per patient per year. DTG/RPV is

also approximately $2,736 less costly than dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) ($15,464 per patient per year) and $4,204 less costly than elvitegravir/cobicistat/TAF/FTC ($16,932 per patient per year).

The manufacturer submitted a cost-utility analysis based on a hybrid decision tree Markov health state–transition model comparing DTG/RPV with other ARV regimens in adults with virologically suppressed HIV-1 infection. Patients in the model transitioned between a total of six therapy lines (three ARV therapy lines and three salvage therapies). Markov health states within each therapy line were defined according to HIV-1 viral load and CD4 cell count. The movement of patients between different viral load and CD4 cell count states within the model was determined by a series of transition matrices, which were generated by adjusting published summary statistics of the change in CD4 cell count by monthly viral suppression probabilities obtained from 48-week suppression probability estimates from the SWORD trials for the DTG/RPV and cARV efficacy profiles, or the published literature for all other efficacy profiles. The analysis was run over a lifetime time horizon (approximately 120 years) using a monthly cycle length, and it was based on the perspective of the Canadian public health care payer. In the probabilistic analysis, the manufacturer reported that DTG/RPV was less costly (savings of at least $42,469) and led to worse outcomes (loss of approximately 0.09 QALYs) than all other ARV regimens. Based on a sequential analysis of the manufacturer's base case, DTG/RPV is a cost-effective option, unless a decision-maker is willing to pay at least $477,574 for a gain of one QALY. At willingness-to-pay thresholds equal to or greater than $477,574 for a QALY gain, RPV/TAF/FTC is the optimal therapy and all other ARV regimens were dominated (associated with greater total costs and no additional QALYs).

CDR identified the following limitations with the submitted economic model:

- Modelling may not reflect the individualized nature of HIV treatment and may overestimate the cost savings associated with DTG/RPV. Although the manufacturer attempted to model multiple sequences of treatment over patients' lifetimes to capture downstream treatment and health care costs after switching to DTG/RPV, there is significant uncertainty with respect to which patients might switch to DTG/RPV, why patients may switch from DTG/RPV and when, and subsequent treatment efficacy.
- The model's functionality relied on the use of complex coding and a separate data repository file, which ultimately resulted in a lack of transparency and reduced model flexibility.

The magnitude of cost savings associated with DTG/RPV is unclear and could not be verified by CDR, owing to the complexity of the submitted model. However, as reported by the manufacturer, DTG/RPV is associated with lower total costs and fewer QALYs compared with other ARV regimens. Therefore, potential cost savings resulting from switching to DTG/RPV may be realized at the expense of reduced population health (a loss of 0.09 QALYs, as predicted by the manufacturer).

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

May 16, 2018 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None.