CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

DOLUTEGRAVIR/LAMIVUDINE (DOVATO — ViiV Healthcare ULC)
Indication: As a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents 12 years of age and older and weighing at least 40 kg.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that dolutegravir/lamivudine (DTG/3TC) be reimbursed as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older and weighing at least 40 kg, only if the following conditions are met.

Conditions for Reimbursement

Initiation Criteria

The patient must be naive to any antiretroviral therapy (ART) and have an HIV-1 viral load ≤ 500,000 copies/mL.

Prescribing Conditions

The patient must be under the care of a practitioner experienced in the care of patients with HIV.

Pricing Conditions

The cost of DTG/3TC should not exceed the total drug plan cost of treatment with the least costly alternative regimen used for the treatment of HIV-1, including the individual components used in combination.

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Reasons for the Recommendation

1. Two identically designed, phase III, randomized, double-blind, multi-centre, parallel group, active-controlled, noninferiority trials in treatment-naive adults with HIV-1 infection and with an HIV-1 ribonucleic acid (RNA) viral load of 1,000 copies/mL to ≤ 500,000 copies/mL (GEMINI-1, N = 719, and GEMINI-2, N = 722) compared a two-drug regimen of DTG + 3TC with a three-drug regimen of DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). The DTG + 3TC combination was demonstrated to be noninferior to DTG + TDF/FTC for achieving viral suppression (proportion of patients with an HIV-1 viral load < 50 copies/mL at week 48) using an FDA-approved noninferiority margin of 10%.
2. At the submitted price, the single-tablet formulation of DTG/3TC is more costly than the individual components. While CADTH reanalysis of a cost-utility model submitted by the manufacturer suggests that DTG/3TC is associated with lower costs and greater quality-adjusted life-years (QALYs) than studied comparators, these results are uncertain due to limitations intrinsic to the model structure, the limitations of the network meta-analysis (NMA) that informed clinical effectiveness estimates, and uncertainty regarding the long-term durability (> 48 weeks) of viral suppression with DTG/3TC. Further, this analysis was based on publicly available prices for all therapies and may not reflect current drug plan costs.

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 DTG/3TC in a manner similar to other HIV-1 treatment regimens.

Discussion Points

- The committee discussed that there is no unmet need for another antiretroviral 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.
- The committee discussed that in the ASPIRE trial (N = 90), results of the primary analysis suggested that in virologically suppressed adult patients with HIV-1 infection, switching to separate tablets of DTG + 3TC was demonstrated to be noninferior to continuing their three-drug ART regimen based on the proportion of patients with treatment failure at week 24, using a noninferiority margin of 12%. However, the committee noted that ASPIRE was associated with numerous limitations, including

the use of an outdated noninferiority margin; the noninferiority margin currently recommended by the US FDA for switch trials is 4%. The committee felt that there was insufficient evidence to make a recommendation for reimbursement in the population of patients with HIV-1 who are currently virologically suppressed on another ART regimen.

- The committee discussed that only 48-week data were available for the trials, and that this is a relatively short duration given the chronic nature of treatment and potential for drug resistance.
- The fixed-dose, single-tablet combination of DTG/3TC at the submitted daily price of $30.44 is more costly by approximately $3.35 than the sum of its individual components ($27.08: DTG, $19.83, and 3TC, $7.25, daily). This difference represents an additional monthly cost of $101.90, or $1,223 annually, per person. This does not take into account the pharmacy dispensing fees of the individual components.

Background

DTG/3TC has a Health Canada indication as a complete regimen for the treatment of HIV-1 infection in adults and adolescents 12 years of age and older and weighing at least 40 kg. DTG is an integrase strand transfer inhibitor (INSTI) and 3TC is a nucleoside reverse transcriptase inhibitor (NRTI). DTG/3TC is available as a single-tablet, fixed-dose combination (FDC) of 50 mg/300 mg, and the Health Canada–approved dosage is one tablet once daily to be taken orally with or without food.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by the CADTH Common Drug Review: a systematic review of randomized controlled trials (RCTs) of DTG 50 mg + 3TC 300 mg and critiques of the manufacturer-provided indirect treatment comparison and 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.

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 held in Toronto and from data collected from a Web-based survey. The following is a summary of key input from the perspective of the patient group.

- Patients living with HIV infection are concerned with access to treatment, barriers to obtaining support services, and the impact of these factors on treatment adherence, mental health, and other determinants of health.
- Patients may be required to change their treatment regimen due to advancements in medication, because of other health complications, or due to development of resistance that results in a need to try other treatment options. Patients feel that HIV infection is a complicated illness that requires treatment options that can be tailored to an individual's needs.
- Patients noted that although current treatments were effective at suppressing viral load, side effects can be problematic, especially with older treatments.
- DTG/3TC is expected to have the benefit of high HIV suppression rates, low potential for drug–drug interactions, and reduced long-term toxicity, which are important to individuals managing lifetime use of HIV antiretroviral treatment. Patients are interested in a new drug composition that is potent against variants resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Clinical Trials

The systematic review included two identical phase III RCTs in treatment-naive adult patients with HIV-1 infection (GEMINI-1, N = 719, and GEMINI-2, N = 722) and one phase III RCT in treatment-experienced adult patients with HIV-1 infection who were virologically suppressed on their current three-drug ART regimen (ASPIRE, N = 90). The GEMINI-1 and GEMINI-2 trials were double-blind, randomized (1:1), noninferiority trials that compared DTG 50 mg + 3TC 300 mg with the active comparator, DTG 50 mg + TDF 300 mg/FTC 200 mg. Randomization was stratified by screening HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) and screening cluster of differentiation 4+ (CD4+) cell count (≤ 200 cells/μL or > 200 cells/μL). The GEMINI trials are ongoing to 148 weeks, with the primary efficacy analysis at 48 weeks, which comprised the manufacturer-provided data. A total of

10% and 8% of DTG + 3TC–treated patients and 8% and 7% of DTG + TDF/FTC–treated patients discontinued the trials in GEMINI-1 and GEMINI-2, respectively. The ASPIRE trial was an open-label, randomized (1:1), pilot, noninferiority switch trial that compared DTG 50 mg + 3TC 300 mg with continuation of patients' three-drug ART. The duration of the ASPIRE trial was 48 weeks, with the primary analysis at 24 weeks. Overall, 8% of patients discontinued the trial. Limitations of the evidence are the small size, open-label design, and use of an outdated noninferiority margin in the ASPIRE trial, the lack of adjustment for multiplicity of secondary outcomes in the statistical analyses, and, in all three trials, use of separate tablet formulations of DTG and 3TC, as opposed to the FDC formulation of DTG/3TC.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, the committee discussed the following:

- proportion of patients with an HIV-1 RNA < 50 copies/mL, as determined by the US FDA-defined snapshot algorithm (primary outcome for GEMINI-1 and GEMINI-2; secondary outcome for ASPIRE)
- proportion of patients with an HIV-1 RNA ≥ 50 copies/mL, as determined by the US FDA-defined snapshot algorithm (primary outcome for ASPIRE was treatment failure defined as a confirmed HIV-1 RNA > 50 copies/mL, loss to follow-up, or treatment discontinuation or modification by week 24)
- change in CD4+ cell counts from baseline
- health-related quality of life was measured by the EuroQol 5-Dimension-5 Level (EQ-5D-5L) questionnaire, which is a standardized, generic, utility-based instrument that provides a profile of patient function and a global health state rating. An overall index score is calculated that ranges from 0 (death) to 1.0 (perfect health); higher scores indicate better health. Overall health is also rated using a visual analogue scale (VAS) that ranges from 0 (worst health you can imagine) to 100 (best health you can imagine); higher VAS scores indicate better overall health status
- resistance of HIV-1 to ART
- change from baseline in lipid, bone, and renal parameters.

Efficacy

Treatment-Naive

- A similar proportion of patients achieved the primary outcome of an HIV-1 RNA < 50 copies/mL at week 48 in GEMINI-1 (90% versus 93%) and GEMINI-2 (93% versus 94%), in the DTG + 3TC versus DTG + TDF/FTC groups, respectively. Based on a 10% noninferiority margin, the results demonstrated that DTG + 3TC was noninferior to DTG + TDF/FTC as the lower bound of the 95% confidence interval (CI) of the adjusted treatment difference was greater than –10% in both GEMINI-1 (–2.6%; 95% CI, –6.7 to 1.5]) and GEMINI-2 (–0.7%; 95% CI, –4.3 to 2.9]). Noninferiority was also observed in the per-protocol population. The proportion of patients with an HIV-1 RNA viral load ≥ 50 copies/mL at week 48 was 4% (n = 13) in the DTG + 3TC group and 2% (n = 6) in the DTG + TDF/FTC group in GEMINI-1 and 2% (n = 7) in each treatment group in GEMINI-2.
- No statistically significant differences in the increase in CD4+ cell count between the DTG + 3TC and DTG + TDF/FTC groups in GEMINI-1 were found at any time point; however, in GEMINI-2, the increase in CD4+ cell count was statistically significant in favour of DTG + 3TC at week 24. The statistical analysis was not adjusted for multiplicity and should be interpreted with consideration of the inflated risk of type I error.
- Health-related quality of life, as measured by the EQ-5D-5L, was reported only as an exploratory outcome in the GEMINI trials. In general, the change from baseline in utility scores and VAS scores were similar in both treatment groups in both trials; however, there is a lack of evidence for validity, reliability, or responsiveness of the EQ-5D-5L in patients with HIV-1 infection and no minimal clinically important difference has been established in this patient population.

- In the GEMINI-1 and GEMINI-2 trials combined, a total of 10 patients (< 1%) met pre-specified criteria for confirmed virologic withdrawal to week 48 (i.e., n = 6 in the DTG + 3TC group and n = 4 in the DTG + TDF/FTC group). None of the patients had emergence of resistance mutations to INSTIs or NNRTIs and all patients were virologic rebounds (not virologic failures).

Treatment-Experienced/Switch

- In the ASPIRE trial, three patients in each treatment group or 6.8% (DTG + 3TC) versus 6.7% (continued ART) met the primary outcome and were defined as treatment failures by week 24. The difference in the proportion of patients meeting this outcome was 0.15% (90% CI, –9.8 to 10.2). Based on a 12% noninferiority margin, the results demonstrated that DTG + 3TC was noninferior to continued ART as the lower bound of the 90% CI of the treatment difference was greater than –12%. Overall, 93% of patients treated with DTG + 3TC versus 91% of patients on continued ART (n = 41 per group) achieved HIV-1 RNA levels < 50 copies/mL at week 24. The corresponding proportions at week 48 were 91% versus 89% (n = 40 per group).
- The median change from baseline to week 48 in CD4+ cell count was 39 cells/μL (interquartile range, –71 to 188) for DTG + 3TC and 28 cells/μL (interquartile range, –36 to 82) for continued ART.
- One patient was classified as a virologic failure in the DTG + 3TC group at week 24 and did not have any emergent reverse transcriptase or INSTI resistance mutations.

Harms (Safety)

Treatment-Naive

- The proportion of patients with AEs was 78% and 74% in the DTG + 3TC groups and 82% and 79% in the DTG + TDF/FTC groups, in GEMINI-1 and GEMINI-2, respectively. The most frequent AEs were headache, diarrhea, nasopharyngitis, and upper respiratory tract infection in both trials. No new safety signals were identified with use of the combination of DTG + 3TC in treatment-naive patients.
- The proportion of patients with serious adverse events (SAEs) was similar in the DTG + 3TC groups (6% and 8%) and the DTG + TDF/FTC groups (6% and 9%), in the GEMINI-1 and GEMINI-2 trials, respectively.
- The proportion of patients who withdrew from the trials due to AEs was 2% in each treatment group in both trials.
- There were no deaths in GEMINI-1; two deaths were reported in GEMINI-2 in the DTG + 3TC group due to Burkitt's lymphoma and acute myocardial infarction.
- Mental health outcomes, and particularly depression, were identified as being important to patients based on the input received. In the GEMINI trials, a low percentage of patients [redacted] experienced depression with no apparent imbalances between treatment groups.
- In both GEMINI trials, changes from baseline to week 48 in various lipid parameters (e.g., total-, LDL-, and HDL-cholesterol) were larger for DTG + 3TC than for DTG + TDF/FTC, whereas changes in bone-related parameters (e.g., serum bone-specific alkaline phosphate, osteocalcin, procollagen 1 N-terminal propeptide, and type-1 collagen C-telopeptide) were larger in the DTG + TDF/FTC group than in the DTG + 3TC group. Similarly, changes in renal-related biomarkers (i.e., serum creatinine, glomerular filtration rate, and urine protein/creatinine ratio) were also larger in the DTG + TDF/FTC group than in the DTG + 3TC group. The magnitude of the treatment differences were unlikely to be clinically relevant.

Treatment-Experienced/Switch

- In the ASPIRE trial, the data reported for AEs demonstrated that no single AE was experienced by more than three patients. There was no information available on SAEs or depression and mental health outcomes.
- One patient in the DTG + 3TC group withdrew due to an AE. No deaths were reported.
- No statistically significant differences were identified in the secondary end points of median change from baseline to week 48 in total-cholesterol, LDL-cholesterol, triglycerides, or creatinine clearance between the DTG + 3TC group and the continued ART group.

Indirect Treatment Comparison

One NMA was submitted by the manufacturer with the aim to compare the efficacy and safety of DTG + 3TC with traditional three-drug ART regimens in treatment-naive adult patients with HIV-1 infection. The NMA included 14 RCTs of three-drug ART regimens that comprised either an INSTI, a boosted protease inhibitor, or an NNRTI as the core drug, combined with two NRTIs as the treatment backbone. Efficacy outcomes were virologic suppression at week 48 and CD4+ cell count change from baseline to week 48, whereas harms outcomes included AEs and SAEs. Results did not provide any evidence for a difference in efficacy or safety between DTG + 3TC and 12 different three-drug ART regimens that are relevant to Canadian clinical practice. A subgroup analysis in patients with a baseline viral load of at least 100,000 copies/mL suggested that DTG + 3TC was no worse than any of the comparators [redacted] for viral suppression at 48 weeks in patients with a high baseline viral load. The sparsity of the evidence networks and the noninferiority design of the primary RCTs precluded the ability of the NMA to establish precise estimates of differences between treatment regimens, thus limiting confidence in the results.

Cost and Cost-Effectiveness

DTG/3TC is an FDC tablet containing 50 mg DTG and 300 mg 3TC to be taken once daily. At the manufacturer-submitted price of $30.44 per tablet, the annual cost of treatment is approximately $11,110 per patient. The daily cost of the individual components of Dovato (DTG + 3TC; $27.08) is less than the DTG/3TC co-formulated FDC tablet.

The manufacturer submitted a cost-utility analysis based on a hybrid decision tree and Markov state transition model to assess the costs and QALYs of treatment with DTG/3TC compared with current standard single-tablet regimens (DTG/abacavir/lamivudine, elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine and bictegravir/emtricitabine/tenofovir alafenamide) and multi-tablet drug regimens (DTG + TDF/FTC) in treatment-naive patients. Health states were defined based on viral load, CD4+ T-cell count, and treatment line with the model allowing patients to receive up to two additional lines of ART before moving on to salvage therapy, on which they would remain until death. The manufacturer-sponsored NMA informed the relative efficacy inputs in terms of virologic (viral load) and immunological response (CD4+ T-cell count), as well as the safety inputs, for all first-line therapies. The manufacturer's base-case model was conducted from the perspective of a Canadian publicly funded health care payer over a lifetime time horizon. In the manufacturer's base case, DTG/3TC was associated with fewer costs and higher QALYs than all comparator regimens (i.e., dominant treatment).

CADTH identified the following key limitations with the manufacturer's submitted economic analysis:

- The NMA used to support the economic evaluation was associated with several limitations (sparsity of the evidence networks and the noninferiority design of the primary RCTs) that led to uncertainty with the estimates of differences between treatment regimens.
- The durability of response and potential for resistant mutations with DTG/3TC is unclear given the short-term nature of clinical studies informing treatment efficacy in the manufacturer's submission.
- For first-line regimens containing TDF, the inclusion of a different cardiovascular disease risk profile was considered inappropriate.
- The time over which the effects of treatment impacts risks of fractures and chronic kidney disease was deemed to be too long.
- Virologic failure is likely to be assessed sooner than 12 months.
- The manufacturer modelled disease progression using CD4+ T-cell counts, which was not considered to be the most appropriate prognostic marker compared with viral load.
- Modelling may not reflect the individualized nature of HIV treatment and may overestimate the cost savings associated with DTG/3TC.

CADTH undertook a reanalysis to remove the differential impact of TDF on cardiovascular disease risk and reduced both the observation period for virologic suppression and the waning period of the impact of treatment on chronic kidney disease and fractures. DTG/3TC dominated all comparators evaluated (i.e., lower expected costs and higher expected QALYs).

CADTH was unable to address several key limitations, including uncertainties in the relative treatment effects in the manufacturer's NMA, uncertainties associated with the model structure, and concerns with the long-term durability of response with DTG/3TC. Clinically relevant first-line treatment options were compared; however, not all first-line ART regimens were considered in the economic evaluation. The model results were primarily driven by drug acquisition costs. The magnitude of the cost savings associated with DTG/3TC remains unclear given the individualized nature of therapy (particularly relating to the timing and reasons for treatment switching), and the analyses that were based on the list prices for the comparator, which may not reflect confidential pricing negotiations (such as any existing product listing agreements).

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.

July 17, 2019

Regrets

None

Conflicts of Interest

None