

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Cabotegravir Tablets, Cabotegravir Extended-Release Injectable Suspension and Rilpivirine Extended-Release Injectable Suspension

(VOCABRIA, CABENUVA — ViiV Healthcare ULC)

Indication: HIV-1 infection

RECOMMENDATION

The CADTH Canadian Drug Expert Committee recommends that the cabotegravir plus rilpivirine regimen be reimbursed for the treatment of HIV-1 infection in adults who are virologically stable and suppressed, only if the following conditions are met.

Conditions for Reimbursement

Initiation Criteria

1. Patients initiating treatment with cabotegravir oral tablets in combination with rilpivirine tablets must:
 - 1.1. be 18 years of age or older
 - 1.2. have virologic suppression, defined as an HIV-1 ribonucleic acid level (viral load) less than the lower limit of quantification (typically 50 copies/mL).

Renewal Criteria

1. Response to treatment with the cabotegravir plus rilpivirine injections should be assessed every six months. A response to treatment is defined as maintenance of virologic suppression (as defined in Initiation Criteria 1.2).

Discontinuation Criteria

1. Treatment with the cabotegravir plus rilpivirine regimen should be discontinued if there is evidence of any of the following:
 - 1.1. sustained loss of virologic suppression (as defined in Initiation Criteria 1.2)
 - 1.2. development of resistance to either component of the drug regimen
 - 1.3. adverse events leading to lack of tolerability of either component of the drug regimen
 - 1.4. lack of adherence to either component of the treatment regimen.

Prescribing Conditions

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

Pricing Conditions

1. The cost of cabotegravir plus rilpivirine should not exceed the total drug plan cost of treatment with the least costly alternative regimen reimbursed for the treatment of HIV-1 in adults.

This document was originally issued on July 22, 2020 and was revised on September 9, 2020 to correct an error in the Costs and Cost Effectiveness section.

Service Line: CADTH Drug Reimbursement Recommendation
 Version: 1.1
 Publication Date: September 9, 2020
 Report Length: 10 Pages

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines*.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Cabotegravir Tablets, Cabotegravir Extended-Release Injectable Suspension and Rilpivirine Extended-Release Injectable Suspension (VOCABRIA, CABENUVA — ViiV Healthcare ULC)

Indication: HIV-1 infection

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that the cabotegravir plus rilpivirine regimen be reimbursed for the treatment of HIV-1 infection in adults who are virologically stable and suppressed, only if the following conditions are met.

Conditions for Reimbursement

Initiation Criteria

1. Patients initiating treatment with cabotegravir oral tablets in combination with rilpivirine tablets must:
 - 1.1. be 18 years of age or older
 - 1.2. have virologic suppression, defined as an HIV-1 ribonucleic acid (RNA) level (viral load) less than the lower limit of quantification (typically 50 copies/mL).

Renewal Criteria

1. Response to treatment with the cabotegravir plus rilpivirine injections should be assessed every six months. A response to treatment is defined as maintenance of virologic suppression (as defined in Initiation Criteria 1.2).

Discontinuation Criteria

1. Treatment with the cabotegravir plus rilpivirine regimen should be discontinued if there is evidence of any of the following:
 - 1.1. sustained loss of virologic suppression (as defined in Initiation Criteria 1.2)
 - 1.2. development of resistance to either component of the drug regimen
 - 1.3. adverse events (AEs) leading to lack of tolerability of either component of the drug regimen
 - 1.4. lack of adherence to either component of the treatment regimen.

Prescribing Conditions

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

Pricing Conditions

1. The cost of cabotegravir plus rilpivirine should not exceed the total drug plan cost of treatment with the least costly alternative regimen reimbursed for the treatment of HIV-1 in adults.

Reasons for the Recommendation

1. CADTH reviewed two phase III, randomized, open-label, multi-centre, active-controlled, noninferiority trials conducted in adults with HIV-1 infection. FLAIR enrolled patients who were antiretroviral (ART) naive (who were subject to an induction phase during which they received treatment with oral ART) whereas ATLAS enrolled patients who were ART experienced who were on a stable ART regimen. In both trials, patients who were virologically suppressed were randomized to switch to either the cabotegravir plus rilpivirine regimen or continue their current oral ART therapy. The cabotegravir plus rilpivirine regimen demonstrated noninferiority to the comparative oral ART regimens for meeting the virologic failure outcome (proportion of patients with an HIV-1 viral load \geq 50 copies/mL) at week 48 using a noninferiority margin of 6%.
2. At the submitted price, the cabotegravir plus rilpivirine regimen (average daily cost = \$39.76) is more costly than the least costly US Department of Health and Human Services–recommended complete oral ART regimen (dolutegravir [Tivicay] plus

emtricitabine and tenofovir disoproxil fumarate [Truvada], daily cost = \$27.14). The results of the sponsor's cost-utility analysis suggest that, based on the clinical evidence, cabotegravir plus rilpivirine is associated with lower costs and greater quality-adjusted life-years (QALYs) than the pooled comparator. CDEC, however, found significant uncertainty associated with the predicted QALY gains. CADTH was unable to address limitations in the sponsor's model structure and uncertainty regarding the long-term durability (> 48 weeks) of viral suppression with cabotegravir plus rilpivirine. Additionally, the lack of information on the potential costs associated with the administration of injections of cabotegravir plus rilpivirine and the use of a pooled combination of oral ART regimens as a single comparator increased the uncertainty associated with the results.

Implementation Considerations

- The cabotegravir plus rilpivirine regimen should only be used in patients who are virologically stable and suppressed with a confirmed diagnosis of HIV-1; this regimen is not approved for use as pre-exposure prophylaxis to reduce the risk of acquiring HIV-1.
- Cabotegravir oral tablets are supplied in bottles of 30 tablets. CDEC noted that some patients may require treatment with cabotegravir tablets (in combination with the rilpivirine tablets) beyond 30 days before switching to the once-monthly intramuscular injections. In both the FLAIR and ATLAS trials, patients received oral cabotegravir and rilpivirine for at least 28 days with an average of 39 days.
- CDEC suggested that, given the potential additional financial burden on the public health care system to administer the cabotegravir and rilpivirine injections, the cost of administration should be financed by the sponsor to support the implementation of the cabotegravir plus rilpivirine regimen.

Discussion Points

- CDEC discussed how the cabotegravir plus rilpivirine regimen might address the unmet needs of patients with HIV-1 infection. CDEC could not determine an unmet clinical need for cabotegravir plus rilpivirine given that patients in Canada currently have access to numerous oral treatments. However, CDEC discussed that some patients may prefer the convenience of monthly injections versus daily oral treatment. There is also the potential that a monthly injection-based regimen may improve adherence in patients for whom adherence to a once-daily dosing regimen is a challenge. While patient input supports a preference for a once-monthly injectable treatment option, there is no demonstrable evidence supporting improved adherence with the cabotegravir plus rilpivirine injectable regimen. Therefore, CDEC believes that at an appropriate price, there may be a viable place for the cabotegravir plus rilpivirine 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 the potential for drug resistance.
- Lack of adherence to the once-monthly injections of cabotegravir and rilpivirine would lead to prolonged suboptimal drug levels in the blood, potentially resulting in a significant risk of developing virologic resistance to either component of the therapy and cross-resistance to other integrase strand transfer inhibitors and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs). The clinical expert consulted by CADTH suggested that patients who are not adherent to the once-monthly cabotegravir and rilpivirine injections may be at greater risk for developing resistance than those receiving treatment with daily ART regimens. However, there is no evidence supporting this hypothesis.

Background

The cabotegravir plus rilpivirine regimen consists of separate once-monthly injections with cabotegravir and rilpivirine preceded by an oral lead-in phase during which oral cabotegravir sodium tablets are taken in combination with currently available rilpivirine tablets.

Cabotegravir tablets are indicated in combination with rilpivirine tablets (rilpivirine tablets are marketed in Canada as Edurant) as a complete regimen for the short-term treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA less than 50 copies/mL) as:

- an oral lead-in to assess the tolerability of cabotegravir before initiating cabotegravir and rilpivirine injections
- oral bridging therapy for missed cabotegravir and rilpivirine injections.

Cabotegravir injection with rilpivirine injection is being indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in patients who are virologically stable and suppressed (HIV-1 RNA less than 50 copies/mL).

Cabotegravir is an integrase strand transfer inhibitors and rilpivirine is a NNRTI. The recommended Health Canada dosage for the cabotegravir plus rilpivirine regimen consists of three distinct phases:

1. Oral lead-in phase: One cabotegravir 30 mg tablet taken together with one rilpivirine 25 mg tablet.
2. Initiation injections of cabotegravir plus rilpivirine (600 mg/900 mg, 3 mL each).
3. Continuation injections of cabotegravir plus rilpivirine (400 mg/600 mg, 2 mL each).

Cabotegravir in combination with available rilpivirine tablets are recommended to be administered orally, once daily, with a meal for at least 28 days prior to the initiation of the injections to assess a patient's tolerability to cabotegravir. The final oral doses of cabotegravir and rilpivirine should be taken on the same day injections with cabotegravir plus rilpivirine are started. The recommended initial injection doses of cabotegravir plus rilpivirine in adults are a single 3 mL (600 mg) intramuscular injection of cabotegravir and a single 3 mL (900 mg) intramuscular injection of rilpivirine. Continuation injections should be initiated a month after the initiation injection. One month following the initiation injections, the recommended continuation injection doses of cabotegravir plus rilpivirine in adults are a single 2 mL (400 mg) intramuscular injection of cabotegravir and a single 2 mL (600 mg) intramuscular injection of rilpivirine administered once monthly. Cabotegravir and rilpivirine injections should be administered at separate gluteal sites during the same visit.

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 of cabotegravir plus rilpivirine, and a critique of the sponsor'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

Five patient group submissions were received from the following organizations: the Canadian Treatment Action Council, the AIDS Committee of Ottawa, the Alliance for South Asian AIDS Prevention, Realize Canada, and a joint submission from four nonprofit groups working in sectors of gay and queer men's health with a focus on HIV prevention, including the AIDS Committee of Toronto, MAX (Ottawa), the Edmonton Men's Health Collective (Edmonton), and the Community-Based Research Centre (a national organization based in Vancouver). Patient perspectives were obtained from a consultation workshop in Toronto, online surveys, and informally from staff and patients through personal experiences and community-based work. The following is a summary of key input from the perspective of the patient groups.

- Patients are generally able to manage their symptoms and disease progression; however, they are more susceptible to inflammation and noninfectious comorbidities such as renal failure, kidney, liver, and cardiovascular diseases at an earlier age. Patients indicated that stigma, discrimination, and the resulting stress are major obstacles to their well-being.
- The physical and mental state of patients 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 the availability of resources. Patients with increased vulnerability and marginalization are particularly affected by the non-equitable distribution of resources; these patients include rural patients (who often face challenges related to travel and access to health professionals), those with low socioeconomic status, immigrants, the homeless, and those struggling with addictions.
- Patients noted that their treatments were generally effective at suppressing viral load and resulted in improved health-related quality of life (HRQoL) and ability to engage in daily activities. Adhering to a daily medication is a challenge according to patients, which is, in part, attributable to medication fatigue. 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 expectations from cabotegravir plus rilpivirine were similar across all five submissions. Patients welcomed the idea of a once-monthly injection, which is expected to reduce stigma by providing patients with more privacy and discretion around living with HIV. In addition, patients expected that a reduction in pill burden would improve adherence and consequently improve viral suppression. One patient group included the experience of patients taking cabotegravir plus rilpivirine. These patients reported having fewer side effects, and the ability to be more socially engaged both in the workplace and their private lives, which led to improved self-esteem. Other notable expectations from a new drug include the ability to be administered privately, and that it not be required to be taken with food.
- The joint submission from the AIDS Committee of Toronto, MAX, the Edmonton Men's Health Collective, and the Community-Based Research Centre also brought forward a concern about a lack of service providers to provide injections and questions about the implementation of cabotegravir plus rilpivirine.

Clinical Trials

The CADTH systematic review included two similarly designed open-label, randomized (1:1), noninferiority switch trials, FLAIR (N = 566) and ATLAS (N = 618), which compared the cabotegravir plus rilpivirine regimen with continuation of patients' oral ART regimen. Both trials were conducted in adult patients with HIV-1 infection who were virologically suppressed (HIV-1 RNA less than 50 copies/mL). Notably, FLAIR enrolled patients who were ART naive whereas ATLAS enrolled patients who were ART experienced who were on a stable ART. However, patients in both trials initiated the cabotegravir plus rilpivirine regimen after viral suppression with ART was achieved. In FLAIR, patients underwent a 20-week induction period following screening, during which they received dolutegravir with abacavir and lamivudine or dolutegravir with a non-abacavir nucleoside reverse transcriptase inhibitor (NRTI) backbone to lower their viral load below 50 copies/mL. Patients who achieved viral suppression were randomized in the maintenance phase to continue their current ART or switch to the cabotegravir plus rilpivirine regimen. In ATLAS, patients who were virologically suppressed were randomized to continue current ART or to switch to the cabotegravir plus rilpivirine regimen immediately after the screening phase. Randomization was stratified by sex at birth (both trials), HIV-1 RNA level at baseline (FLAIR only), and baseline third drug class (ATLAS only). In both trials, the once-monthly cabotegravir plus rilpivirine injection or oral ART regimen was continued for 96 to 100 weeks (currently ongoing), with the primary efficacy analysis at 48 weeks. A total of 9% and 8% of patients treated with cabotegravir plus rilpivirine and 8% and 6% of patients treated with ART discontinued during the maintenance phase in FLAIR and ATLAS, respectively.

Limitations of the evidence are the open-label study design, the use of HRQoL measures with limited validity in patients with HIV, the lack of adjustment for multiplicity of secondary outcomes in the statistical analyses, and limited long-term data beyond 48 weeks.

Outcomes

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

- Virologic failure: Proportion of patients with an HIV-1 RNA of 50 copies/mL or greater at week 48, as determined by the US FDA-defined snapshot algorithm
- Virologic suppression and success: Proportion of patients with an HIV-1 RNA of lower than 50 copies/mL at week 48, as determined by the US FDA-defined snapshot algorithm
- Change in cluster of differentiation 4 plus (CD4+) cell count from baseline
- A number of patient-reported HRQoL end points were assessed, including HIV Treatment Satisfaction Questionnaire Status (HIVTSQs) and Changed Version (HIVTSQc), Perception of Injection (PIN), Chronic Treatment Acceptance Questionnaire (ACCEPT), HIV/AIDS Targeted Quality of Life (HAT-QoL), 12-Item Short Form Health Survey (SF-12), and Numeric Rating Scale (NRS) scores. No minimal important difference was identified in patients with HIV for any of the HRQoL measures.

- The HIVTSQ is an HIV-specific questionnaire that assesses treatment satisfaction in patients with the disease. The scale has two versions, Status and Changed, that are comprised of 10 and 12 items, respectively. Higher scores on the HIVTSQs and HIVTSQc are indicative of a greater level of satisfaction.
 - The PIN questionnaire is a measure of perception of injection-related pain (e.g., injection site pain, anxiety, satisfaction) that has four dimensions and 21 items, of which one domain (acceptability of injection site reactions [ISRs]) was tested statistically. A lower score on the PIN questionnaire indicates a more favourable perception.
 - The ACCEPT is a generic measure of medication acceptance consisting of 25 items and seven domains, of which only one domain was tested in the trials. A greater score on the ACCEPT indicates greater acceptance.
 - The HAT-QoL is an HIV-specific 42-item, nine-dimension instrument adapted to 14 items and three dimensions in FLAIR and ATLAS. Higher scores on the HAT-QoL indicate better function and well-being.
 - The SF-12 is a generic HRQoL measure that is based on the 36-item version of the survey and is categorized into physical and mental component scores. Higher scores on the SF-12 are indicative of improved HRQoL.
 - The NRS is a one-item scale that measures post-injection site pain.
- Resistance
 - Adherence

Virologic failure was the primary efficacy outcome in both trials; the remaining outcomes were considered secondary. The virologic outcomes (virologic failure and suppression), the HIVTSQ, and the PIN were included in the statistical testing hierarchy.

Efficacy

- Overall, the treatment groups in each trial had comparable virologic responses. Virologic failure was seen in 2.1% and 2.5% of patients in the cabotegravir plus rilpivirine and oral ART groups in FLAIR, respectively, and 1.6% and 1.0% of patients in the cabotegravir plus rilpivirine and oral ART groups in ATLAS, respectively. Based on a 6% noninferiority margin, the results demonstrated that cabotegravir plus rilpivirine was noninferior to continuation of oral ARTs, with an adjusted between-groups treatment difference of -0.4% (95% confidence interval [CI], -2.8 to 2.1) in FLAIR and 0.6% (95% CI, -1.2 to 2.5) in ATLAS. Noninferiority was also observed in the per-protocol population.
- The proportion of patients with an HIV-1 RNA viral load less than 50 copies/mL at week 48 was 94% and 93% in the cabotegravir plus rilpivirine group and 93% and 95% in the oral ART group in FLAIR and ATLAS, respectively. Both trials met the pre-specified noninferiority margin of -10%, with treatment differences in FLAIR and ATLAS of 0.4% (95% CI, -3.7 to 4.5) and -3.0% (95% CI, -6.7 to 0.7), respectively. None of the virologic outcomes showed a notable or statistically significant difference by relevant subgroups (sex at birth, baseline HIV-1 RNA level, and CD4+ cell count).
- CD4+ cell count increased at week 48 compared to baseline levels in both trials, regardless of treatment. The average increase in FLAIR was 40.2 cells/mm³ and 79.9 cells/mm³ from baseline in the cabotegravir plus rilpivirine and oral ART groups, respectively. In ATLAS, the mean change from baseline at week 48 was 9.9 cells/mm³ and 19.4 cells/mm³ in the cabotegravir plus rilpivirine and oral ART groups, respectively. However, a statistical test to compare the difference between treatment groups was not conducted.
- Of the HRQoL end points, HIVTSQs and PIN scores were reported as key secondary outcomes. In both trials, there was a slight increase in HIVTSQs score at week 44 in both treatment groups. The adjusted mean differences in HIVTSQs score at week 44 between the two treatment groups were 0.7 (95% CI, -0.4 to 1.9; P = 0.22) and 5.68 (95% CI, 4.37 to 6.98; P < 0.001) in FLAIR and ATLAS, respectively. On the PIN, the acceptability of ISR domain score showed a statistically significant change from baseline to week 48 (mean score change from week 5 = 0.40 and -0.54 in FLAIR and ATLAS, respectively; P < 0.001 in both cases). The statistical analyses of the remaining HRQoL outcomes were not controlled for multiplicity. Overall, a strong and consistent finding was not found for any of the HRQoL outcomes across studies. Further, there is a lack of evidence for validity, reliability, or responsiveness for most of these end points and no established minimal important difference for any of these end points in patients with HIV-1 infection.
- In terms of adherence, 98% of injections were given in the seven-day treatment window, with few instances of missed injections.

- Resistance to the study medications occurred infrequently; there were six cases of treatment-emergent resistance to cabotegravir or rilpivirine in total. In FLAIR, all three patients with confirmed virologic failure (CVF) who received cabotegravir plus rilpivirine injections had treatment-emergent rilpivirine, integrase inhibitor, and cabotegravir resistant mutations. None of the three patients with CVFs who continued on oral ART had treatment-emergent resistance mutations. In ATLAS, all three CVF cases in the cabotegravir plus rilpivirine group had treatment-emergent rilpivirine-resistance mutations leading to decreased virus susceptibility to the drug. In the continued oral ART group, two cases of NRTI and NNRTI-associated mutations were found each, and one case of integrase inhibitor-associated mutations was found.

Harms (Safety)

- The proportion of patients with AEs was 94% and 95% in the cabotegravir plus rilpivirine groups and 80% and 71% in the oral ART groups, in FLAIR and ATLAS, respectively. The increased incidence of AEs in the cabotegravir plus rilpivirine groups was in part attributable to various ISRs resulting from the monthly intramuscular injections (overall frequency 86% and 83% in FLAIR and ATLAS, respectively). The most frequent AEs (incidence of $\geq 10\%$ in any group) were injection site pain, nasopharyngitis, injection site nodule, headache, upper respiratory tract infection, injection site induration, and diarrhea.
- Overall, there were no fatal serious adverse events (SAEs) and the incidence of nonfatal SAEs was low across trials (range = 4% to 6%), with comparable SAE frequencies observed between treatment groups.
- The proportion of patients who withdrew from the trials due to AEs was 4% or less in each treatment group in both trials.
- Two deaths were reported during both studies; one in FLAIR that occurred prior to the start of the cabotegravir plus rilpivirine treatment, and one in ATLAS, due to methamphetamine overdose, in a patient receiving oral ARTs.
- Among notable harms identified in the CADTH review protocol, ISRs were the most frequently reported AEs in patients receiving cabotegravir plus rilpivirine, with more than 80% reporting at least one ISR event. Injection site pain was the most commonly reported ISR (> 75%), followed by injection site nodules (12% to 16%), and induration (10% to 13%). No ISRs were reported as SAEs and withdrawal due to ISRs was low. Mental health outcomes, particularly depression, were identified as being important to patients based on the input received. Psychiatric disorders were reported in 8% and 13% of patients across trials (similar proportion between treatment groups); the frequency of depression was no more than 2% in either treatment group of either trial. Bone, renal, and liver biomarkers remained stable and showed no signs of abnormal patterns over time.

Indirect Treatment Comparisons

No indirect evidence was submitted by the sponsor. An independent search for indirect evidence conducted by CADTH did not find any published indirect evidence that met the inclusion criteria of the CADTH review protocol.

Cost and Cost-Effectiveness

The sponsor submitted the following prices for cabotegravir products: \$26.52 per 30 mg cabotegravir tablet; \$2,418.75 per initiation kit (600 mg cabotegravir injection/900 mg rilpivirine injection); and \$1,209.38 per continuation kit (400 mg cabotegravir injection/600 mg rilpivirine injection). Rilpivirine is \$15.50 per tablet according to the Ontario Drug Benefit Formulary. At these prices, the first-year cost of the cabotegravir plus rilpivirine regimen is \$15,742 per patient; thereafter, the annual maintenance cost is \$14,513 per patient.

The sponsor submitted a hybrid model of Markov state-transition and decision tree processes to assess the cost utility of cabotegravir plus rilpivirine as a complete two-drug regimen (i.e., cabotegravir oral tablets in combination with rilpivirine oral tablets; followed by cabotegravir plus rilpivirine initiation and continuation injections) relative to a pooled oral ART regimen for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA of less than 50 copies/mL). 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 clinical efficacy for cabotegravir plus rilpivirine and combined oral ART were informed by the pooled data from the ATLAS and FLAIR trials. The sponsor's base-case model was conducted from the perspective of a Canadian publicly funded health care payer over a lifetime time horizon (approximately 60 years). As the sponsor's model was not stable at 350 iterations (sponsor's base case), CADTH re-ran the

sponsor's base case at 5,000 iterations and the incremental cost-effectiveness ratio for cabotegravir plus rilpivirine was found to be \$6,815 per QALY gained compared to a pooled combination of oral ART regimens.

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

- Cabotegravir plus rilpivirine was compared to a single comparator consisting of a pooled combination of oral ART regimens. The cost-effectiveness of cabotegravir plus rilpivirine relative to individual ART regimens is unknown.
- The sponsor assumed reduced adherence in the oral ART group only, and consequentially, assumed poor adherence would decrease viral load suppression and increase the probability of viral load rebound. A lack of clinical evidence exists to support these assumptions.
- As the durability of response to cabotegravir plus rilpivirine is unclear, the long-term cost-effectiveness of cabotegravir plus rilpivirine is uncertain.
- The sponsor modelled HIV-related disease progression using CD4+ T-cell count, which, when compared to viral load, was not considered to be an accurate prognostic marker.
- The submitted economic model does not reflect the individualized nature of HIV treatment and may overestimate the cost savings associated with cabotegravir plus rilpivirine.
- Potential administration costs for cabotegravir and rilpivirine injections were excluded, which may have underestimated the total cost of cabotegravir plus rilpivirine.

CADTH undertook a reanalysis that assumed no difference in adherence between cabotegravir plus rilpivirine and oral ARTs but was unable to address the other identified limitations given the model structure and limitations with the data. Compared to pooled oral ART, cabotegravir plus rilpivirine was associated with lower costs and fewer QALYs. The incremental cost-effectiveness ratio for combined oral ART compared with cabotegravir plus rilpivirine was \$37,501 per additional QALY gained.

These results are highly uncertain as CADTH could not address limitations related to the model structure and the durability of treatment effect with cabotegravir plus rilpivirine over the model's time horizon. The cost-effectiveness of cabotegravir plus rilpivirine compared to individual commonly prescribed first-line regimens (such as dolutegravir plus emtricitabine and tenofovir disoproxil fumarate) is unknown, some of which have lower annual drug costs than cabotegravir plus rilpivirine. Additionally, the analysis did not take into account the potential costs associated with the administration of cabotegravir plus rilpivirine.

CDEC Members

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

January 15, 2020 Meeting (Initial)

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None

July 15, 2020 Meeting (Reconsideration)

Regrets

One CDEC member did not attend.

Conflicts of Interest

None