



## CADTH Reimbursement Recommendation

# Fostemsavir (Rukobia)

**Indication:** Human immunodeficiency virus (HIV) type 1

**Sponsor:** ViiV Healthcare ULC

**Final recommendation:** Reimburse with conditions



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# Summary

## What Is the CADTH Reimbursement Recommendation for Rukobia?

CADTH recommends that Rukobia be reimbursed by public drug plans for the treatment of HIV type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant (MDR) HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance, or safety considerations if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Rukobia should be covered for patients living with HIV-1 whose disease does not respond to the majority of antiretroviral therapies (ARVs) available (ARVs in at least 3 classes) because the available ARVs no longer work, for those who cannot tolerate side effects, or for those who have other safety concerns. In addition, patients should have 1 fully active available drug left in no more than 2 ARV classes based on current and/or documented historical resistant testing. Lastly, Rukobia should be covered for patients who have a viral load that suggests poor control of their infection ( $\geq 400$  copies/mL of HIV-1 ribonucleic acid [RNA]).

### What Are the Conditions for Reimbursement?

Rukobia should only be reimbursed if it is initially prescribed by, or in conjunction with, a physician who specializes in the management of HIV-1 infection and if the cost of Rukobia is reduced. Reimbursement of Rukobia should be discontinued if the patient's viral load is not improving, as this suggests that treatment is not working.

### Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that Rukobia reduces viral load better than placebo in patients who have received several anti-HIV-1 regimens in the past, and have an HIV-1 virus that is resistant to many ARV medicines. The clinical trial also suggests that a reduction in viral load was maintained over time and an increase in CD4+ counts was also observed.
- Based on CADTH's assessment of the health economic evidence, Rukobia does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Patients who have received several anti-HIV-1 regimens in the past and have an HIV-1 virus that is resistant to many ARV medicines have few ARV treatment options available. There is a high unmet



# Summary

need for effective treatments for these patients, and Rukobia provides an additional ARV treatment option.

- Based on public list prices, Rukobia is estimated to cost the public drug plans approximately \$19.6 million over the next 3 years.

## Additional Information

### What Is HIV-1 Infection?

HIV-1 is a virus that attacks the body's immune system. As a result, the patient becomes immunocompromised and more likely to get sick from other infections and some cancers. Without adequate treatment, HIV-1 infection can progress to AIDS, which is an advanced and life-threatening stage of the disease. Approximately 62,790 people were living with HIV-1 in Canada in 2020.

### Unmet Needs in HIV-1 Infection

There is no cure for HIV, but patients can live with HIV by controlling their infection with treatment. A subset of patients living with HIV-1 have had experience with several treatments for HIV-1 but have a virus that is resistant to multiple treatments. The HIV-1 infection in these patients cannot be controlled and is at risk of progressing to AIDS. As such, there is a high unmet need for additional treatment options for this group of patients.

### How Much Does Rukobia Cost?

Treatment with Rukobia is expected to cost approximately \$45,854 per patient per year.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that fostemsavir be reimbursed for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in heavily treatment-experienced (HTE) adults with MDR HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance, or safety considerations, only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

Evidence from 1 study that included an 8-day double-blind (DB) phase followed by an ongoing open-label (OL) phase of up to 240 weeks (BRIGHTE; N = 272) demonstrated that treatment with fostemsavir plus optimized background therapy (OBT) resulted in added clinical benefit for patients with MDR HIV-1 infection who are HTE. During the DB phase, the BRIGHTE study demonstrated that, compared with placebo, 8 days of treatment with fostemsavir was associated with a statistically significant and clinically meaningful reduction in viral load (between-groups difference in plasma HIV-1 RNA  $\log_{10}$  copies/mL =  $-0.625$ ; 95% confidence interval [CI],  $-0.810$  to  $-0.441$ ;  $P < 0.0001$ ). During the OL phase, a reduction in viral load was maintained and an increase in CD4+ counts was also observed. Also, there were no clear indications of safety or tolerability issues during the trial. Although analysis of these outcomes over time is limited by the lack of a control group, by attrition, and other sources of missing data over the 240-week follow-up period, patients living with MDR HIV-1 who are HTE have limited options for ongoing treatment. Fostemsavir is a first-in-class ARV therapy for this patient population that can potentially fulfill this treatment gap. In addition, patients reported that they need additional treatment options that are safe, effective, long-lasting, accessible, and likely to reduce disability or premature death. Evidence from the BRIGHTE trial suggests that fostemsavir may meet some of these needs (safety and efficacy).

Using the sponsor-submitted price for fostemsavir and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for fostemsavir plus OBT was \$469,086 per quality-adjusted life-year (QALY) compared with OBT alone. At this incremental cost-effectiveness ratio, fostemsavir is not cost-effective at a \$50,000 per QALY willingness-to-pay threshold for adults with MDR HIV-1 infection who are HTE and for whom it is otherwise not possible to construct a suppressive antiviral regimen. A price reduction is required for fostemsavir plus OBT to be considered cost-effective at a \$50,000 per QALY threshold.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. In patients who demonstrate resistance, intolerability, and/or contraindications to ARVs in at least 3 classes.	The BRIGHTE trial showed that patients treated with fostemsavir who had demonstrated resistance, intolerability, and/or contraindications to ARVs in at least 3 classes experienced a reduction in viral load compared	—

Reimbursement condition	Reason	Implementation guidance
	to patients who received placebo (a failing ARV regimen).	
2. In patients who have 1 fully active and available drug in 2 or fewer ARV classes based on current and/or documented historical resistance testing, taking into account tolerability and other safety concerns.	Fostemsavir is indicated for patients for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance, or safety considerations. The BRIGHTE trial provided evidence of safety and efficacy of fostemsavir in patients who had 1 fully active and available drug in 2 or fewer ARV classes.	—
3. In patients who have an HIV-1 RNA count of $\geq 400$ copies/mL.	The BRIGHTE trial showed that patients treated with fostemsavir who had an HIV-1 RNA count of $\geq 400$ copies/mL at baseline experienced a reduction in viral load compared to patients who received placebo (a failing ARV regimen).	—
<b>Discontinuation</b>		
4. Fostemsavir should be discontinued if a patient's HIV-1 RNA level does not indicate an improvement in viral load.	The clinical expert indicated that it would be reasonable to discontinue treatment if there was no response to fostemsavir.	—
<b>Prescribing</b>		
5. Fostemsavir must be initially prescribed by, or in conjunction with, a physician who specializes in the management of HIV.	This is meant to ensure that fostemsavir is prescribed for appropriate patients.	Although treatment should be initiated by a health care professional experienced in the management of HIV, patients could be managed in a community care setting where they are followed by a physician or nurse practitioner trained to manage treatment.
<b>Pricing</b>		
6. A reduction in price	CADTH was unable to perform reanalysis due to structural issues within the sponsor's model. Based on the sponsor's submitted results, a price reduction of at least 94% is required to achieve an ICER of \$50,000 per QALY.	—

ARV = antiretroviral; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RNA = ribonucleic acid.

## Discussion Points

- CDEC discussed the prevalence of MDR HIV-1 in patients who are HTE and though living with HIV-1 is not a rare condition, patients with MDR HIV-1 who are HTE represent a very small population of patients living with HIV-1 in Canada. The clinical expert estimated that this patient population likely represents between 1% to 4% of patients receiving treatment for HIV. Furthermore, this

patient population is defined by not having enough active or partially active classes available to construct a suppressive treatment regimen; therefore, there is a high unmet need for an additional treatment option.

- Given the presence of viral resistance in the HTE population, and that fostemsavir is intended for use as a last resort for patients, there are challenges in defining a lack of treatment response. Clinical judgment and expertise is also required to appropriately interpret the clinical results and advise on the best approach to care in this patient population.
- CDEC discussed potential reasons for discontinuation of fostemsavir. In the BRIGHT trial, approximately 65% of the patients randomized to fostemsavir achieved at least a 0.5 log<sub>10</sub> reduction in HIV-1 RNA by day 8. Given the short duration of follow-up and the assumption that more patients would achieve a reduction in HIV-1 RNA beyond 8 days of treatment, the committee discussed that discontinuation may be considered for patients who do not achieve at least a 0.5 log<sub>10</sub> reduction in HIV-1 RNA after 3 months of treatment.
- The committee noted the high degree of uncertainty in the pharmacoeconomic analysis. The underlying uncertainty in the sponsor's method for estimating change in CD4+ status resulted in 36% of sampled incremental QALY results being less than 0. The committee did not find any evidence that fostemsavir plus OBT would produce worse patient outcomes than OBT alone. This figure was interpreted as reflecting the degree of uncertainty that fostemsavir would not be cost-effective at any willingness-to-pay threshold.

## Background

HIV consists of 2 subtypes, HIV-1 and HIV type 2, and is transmitted via bodily fluids such as blood, semen, and genital secretions, as well as in breast milk. Infection with HIV-1 selectively destroys CD4+ immune cells, resulting in a gradual weakening of the immune system over time. Eventually, the patient with HIV-1 becomes immunocompromised and highly susceptible to opportunistic infections. HIV-1 can progress to AIDS, which is ultimately fatal if untreated. According to the Public Health Agency of Canada (PHAC), in 2020 there were an estimated 62,790 patients living with HIV in Canada.<sup>2</sup> Among those with HIV, it is estimated that 90% were diagnosed, and of those diagnosed, 87% were on treatment and 95% had a suppressed viral load. There are also specific populations that are disproportionately impacted by HIV, such as Indigenous people and those who inject drugs.

HIV-1 is treated using combinations of antivirals because combination therapy is necessary to achieve sustained control of HIV-1 viremia as resistance occurs quickly when HIV-1 is exposed to insufficient treatment regimens, according to the clinical expert consulted by CADTH. There are 4 main classes used in these combination regimens, and typically 2 to 3 of these classes are used in each ARV regimen according to the clinical expert, who also noted that infection control is achievable in most patients using combinations involving these classes; however, there are 2 additional classes that can be used as rescue therapies in patients experiencing issues with resistance to the conventional 4 classes. The goal of therapy, according to the clinical expert consulted by CADTH on this review, is to control viral replication and/or viremia, which

in turn prevents HIV disease progression, prolongs life, prevents transmission, reduces the incidence of HIV-affected chronic diseases, and improves quality of life. According to the clinical expert consulted by CADTH on this review, patients with HIV are defined as being HTE if they have 2 or fewer available classes of fully active medications (i.e., with expected ability to treat that patient). These classes tend to be second line, according to the clinical expert, because of their lower tolerability, higher burden of side effects, and the challenges they present with administration, all of which complicate the safety and stability of long-term therapy.

Fostemsavir is a first-in-class inhibitor of HIV-1 attachment and viral entry. It is indicated for adult patients with HIV-1 who are HTE and have MDR HIV-1, and for whom it is otherwise not possible to construct a suppressive antiviral regimen due to resistance, intolerance, or safety considerations. Fostemsavir, which is a prodrug for temsavir, is available as an extended-release tablet and administered orally at a dosage of 600 mg twice daily (in addition to standard of care).

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 pivotal, phase III trial in patients with chronic HIV-1 who were ARV-experienced with resistance, intolerability, and/or contraindications to ARVs in at least 3 classes
- patients' perspectives gathered by 1 patient group, the Community-Based Research Centre (CBRC)
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with HIV-1
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

One patient group submitted input, the CBRC, which is a non-profit charitable organization based in Vancouver, British Columbia, that promotes the health of people of diverse sexualities and genders through research and intervention. The CBRC collected information via Sex Now, a community-based research initiative and Canada's largest running survey of gay, bisexual, queer men (cis and trans), non-binary, and Two-Spirit people's health in 2021 (n = 325) and 2022 (n = 144).

The group said the outcome of untreated HIV is disability and premature death. According to the input, as the most stigmatized disease worldwide, people living with HIV are too often viewed by society, public health, governments, the legal system, and researchers as a vector of disease. As a result, the living experience of someone with HIV is reduced to whether they can transmit HIV, rather than it being viewed as a health

condition that is part of lived experience with the disease. Pill burden and medication adherence is a challenge for many and certain socioeconomic factors and/or social determinants of health (e.g., housing and food insecurity makes it more challenging). About a third of Sex Now 2021 survey respondents said that they experienced a reduction in stigma, shame, and rejection, and about a third experienced an improvement in mental, social, sexual well-being, because of the U = U campaign. However, nearly 20% of respondents felt pressured to take medication or maintain an undetectable viral load due to the U = U campaign. Moreover, the Sex Now 2021 survey (which was conducted online) showed a positive correlation between a suppressed viral load and having a health care provider as well as ease of taking medicine. According to Sex Now 2022 survey conducted at Pride festivals and other queer spaces, 19% of people said they prefer taking daily oral pills, whereas 47% said they prefer injectables. This result shows a strong desire among the 2SLGBTQ+ community for innovation in HIV treatment (e.g., long-acting drugs to reduce the burden of taking medication).

The input stated that for people living with HIV who are HTE, there are no other treatment options. The patient group feel that it would be highly unethical for this drug to not be available because untreated HIV can lead to disability and premature death and the likelihood of passing on HIV when sexually active or sharing injection supplies with others increases. In general, this population faces barriers in the social determinants of health, and the input suggests that considerations need to be made for how pharmaceutical companies can find ways to support medication adherence outside of the medical model (e.g., social supports, income supports, food security, housing security, mental health support).

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by a clinical specialist with expertise in the diagnosis and management of patients living with HIV.

### Unmet Needs

According to the clinical expert consulted by CADTH on this review, not all patients respond to available treatments. They also indicated that many patients with prior exposure to ARVs develop resistance to individual medications and whole classes of medications as a function of the type of resistance mutations. The clinical expert noted that patients with increasing ARV resistance and those with multiple classes of resistance experience increasingly significant negative outcomes related to HIV (including lower life expectancy, higher burden of opportunistic and other chronic diseases, and greater treatment-related complications).

According to the clinical expert consulted by CADTH, there continue to be patients for whom medication intolerance or adverse reactions (including lipodystrophy, neuropsychiatric consequences, weight gain,

metabolic disease) are a consistent barrier to use; therefore, more treatments are needed to address these gaps.

The clinical expert noted that by definition there are limited treatment options in the setting of HTE, because all or nearly all of the safe, effective, and easily administered regimens have lost any efficacy due to resistance. Therefore, the clinical expert noted that clinicians are forced to use therapies with lower viral efficacy, greater associated harms (in the form of adverse events [AEs]), and which are more difficult to administer (i.e., subcutaneous injections). All of these factors make treatment adherence challenging to maintain in the long term. In summary, the clinical expert noted that access to well-tolerated, effective new antiviral drugs from novel classes are needed to improve care for this group.

### **Place in Therapy**

According to the clinical expert consulted by CADTH on this review, fostemsavir would be used for patients who are HTE, or other patients for whom there are limited options for treatment as a result of underlying disease state or drug resistance. The clinical expert noted that fostemsavir would provide a new class of anti-HIV therapies for use in treatment-experienced patients with drug-resistant HIV infection, for whom outcomes are poor. The clinical expert went on to note that a well-tolerated oral treatment for this patient population would be used in cases of drug resistance. They also noted that, currently, patients with resistance to 3 or more classes of ARV therapy typically require medications from 3 or 4 classes and using multiple modalities (combining oral and injectable) therapies, or they are dependent on access to participation in clinical trials. Therefore, according to the clinical expert, new oral therapies are needed to improve virological response, clinical outcomes, and adherence to treatment to manage HIV in this context.

### **Patient Population**

According to the clinical expert consulted by CADTH on this review, patients who are treatment experienced and have MDR HIV are those who would respond to treatment with fostemsavir. These patients are in need of such interventions.

The clinical expert noted that HIV specialists would identify patients for whom fostemsavir would be appropriate to use based on clinical history, treatment history (i.e., ARV therapy exposure and outcomes), and resistance testing of the patient's virus. According to the clinical expert, these patients are not difficult to identify in clinical practice, and the testing required to facilitate treatment is already routinely performed in their care and management. The expert also noted that it is possible to identify the patients who would most likely respond using the previously mentioned assessments.

### **Assessing Response to Treatment**

According to the clinical expert consulted by CADTH on this review, viral load is the most important test to determine response to treatment. Clinical response (e.g., resolution of disease-related symptoms, immune reconstitution, rate of opportunistic infections, survival) will add supplemental evidence of treatment response.

The clinical expert noted that a clinically meaningful response to treatment would be improvement or suppression of viral load or recovery of immune function (predominantly measured by CD4+ count),

alongside resolution or stability in HIV-related symptoms (if present), presence and/or prevention of opportunistic infections, and improvement or stability in related chronic diseases (e.g., anemia, thrombocytopenia) if they are present. The treatment outcome is unlikely to vary across physicians.

### Discontinuing Treatment

The clinical expert consulted by CADTH on this review noted the following factors that would be considered when deciding to discontinue fostemsavir:

- lack of response to treatment and/or evidence of resistance based on phenotypic or genotypic resistance testing
- AEs (i.e., untreatable or irreversible side effects that render the medication intolerable to the patient, or those that are too life- or organ-threatening to continue, such as hypersensitivity, liver disease, or unstable cardiac arrhythmia)
- patient preference.

### Prescribing Conditions

According to the clinical expert consulted by CADTH on this review, specialty clinics (e.g., infectious diseases, internal medicine), and in some cases community clinics with HIV expertise, are the most appropriate settings for treatment and monitoring of patients with HIV who are HTE. The clinical expert noted that in Canada the majority of patients with HIV are managed in these settings.

### Clinician Group Input

No clinician group input was received for this submission.

### Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Considerations for initiation of therapy</b>	
The indication corresponds to the unstable and unsuppressed HTE population with 4-class resistance with 0 to 2 fully active classes of treatment remaining, for whom a suppressive regimen cannot be constructed due to resistance, intolerance, or safety considerations.	
Please provide clarity or define what would be acceptable intolerance and safety considerations?	The clinical expert noted that although safety issues can be measured more objectively, the impact of tolerability is based on agreement between the physician and the patient, as well as the patient’s ability to mitigate side effects. CDEC agreed with the clinical expert, noting that no evidence was provided for more specific guidance regarding intolerance.

Implementation issues	Response
<p>What parameters are used to measure resistance?</p>	<p>The clinical expert noted that resistance is measured objectively, and resistance profile and genotyping is assessed based on laboratory assessments. There is also clinically defined resistance, where a patient's disease is not responding to the drug (e.g., viral load is not reduced) and in these patients, the most common issue is nonadherence to therapy.</p> <p>CDEC agreed with the clinical expert.</p>
<b>Considerations for discontinuation of therapy</b>	
<p>Virologic response (HIV-1 RNA &lt; 40 copies/mL) was assessed at each time point using the FDA Snapshot algorithm, which considers only HIV-1 RNA level at the visit of interest.</p> <p>The indication is for combination use with other ARVs.</p> <p>End points in the study included virologic response, change in CD4+ cell count, and gp120 polymorphisms.</p>	
<p>The clinical report mentions clinically meaningful CD4+ T cell. Could this be defined and at what point would Rukobia be discontinued?</p>	<p>The clinical expert consulted by CADTH on this review noted that CD4+ count is unlikely to be used to determine whether or not a patient should discontinue therapy. CDEC agreed with the clinical expert; however, it also noted that viral load may be used to determine whether a patient should discontinue therapy.</p>
<p>Virologic response (HIV-1 RNA &lt; 40 copies/mL) was assessed at each time point using the FDA Snapshot algorithm. Does this align with how virologic response that assessed in Canada?</p>	<p>The clinical expert noted that virologic response is typically assessed every 6 months in patients with stable disease. In patients who are changing therapies, virologic response could be assessed every 1 to 3 months. When initiating patients on a new treatment, or if their disease is unstable, assessment of virologic response is typically limited by availability of the patient and what is permitted by jurisdictions; therefore, an assessment every 4 to 6 weeks would be sufficient.</p> <p>CDEC agreed with the clinical expert.</p>
<p>Would both the HIV-1 RNA and CD4+ T-cell count be used to determine discontinuation and what at what levels would this be? Gp120 polymorphism was an additional end point, what is the clinical significance of this in the use Rukobia?</p>	<p>The clinical expert noted that virologic response, targeting &lt; 40 copies/mL or &lt; 50 copies/mL (depending on the assay used) would be used to determine response. The clinical expert went on to note that a higher viral load may be tolerated in this HTE population if a clinical response is observed (so a target of 250 copies/mL to 1,000 copies/mL).</p> <p>The clinical expert noted that gp120 is important for establishing HIV subtype and susceptibility in relation to resistance to the drug. The clinical expert went on to note that they had no concerns with fostemsavir in this regard, based on the results from the BRIGHT trial.</p> <p>CDEC agreed with the clinical expert that viral load could be used to assess response to treatment and therefore could be used to determine whether treatment should be discontinued (due to a lack of response).</p>
<p>If the patient can no longer take their current ARV therapy due to intolerance or safety considerations is Rukobia discontinued or can a patient continue on with Rukobia?</p>	<p>The clinical expert noted that patients who need to discontinue their ARV therapy due to intolerance and/or safety would not continue on fostemsavir as monotherapy.</p> <p>CDEC agreed with the clinical expert.</p>

Implementation issues	Response
<p>What would be a reasonable amount of time a patient would be on Rukobia to see a clinical meaning full response before discontinuing?</p>	<p>The clinical expert noted that a trial of 3 months to 6 months would be used to assess for a clinically meaningful response, varying depending on the patient's viral load. CDEC agreed with the clinical expert.</p>
<p>Based on the clinical trial the sponsor claims that fostemsavir undoubtedly provides substantial clinical and economic certainty for patients with MDR HIV who are HTE, clinicians, and payers for a minimum of 5 years, per the 240-week data.</p> <p>An ARV regimen is typically composed of 2 to 3 fully active ARV drugs from 2 different classes to suppress HIV RNA to below assay quantification limits (&lt; 20 copies/mL to 50 copies/mL).</p> <p>An undetectable viral load is clinically presented as an HIV-1 RNA of less than 50 copies/mL.</p> <p>Based on the length of the study, would treatment continue past 5 years if the patient demonstrates progressive sustained virological efficacy?</p>	<p>The clinical expert consulted by CADTH on this review noted that treatment would indeed continue past 5 years if the patient demonstrated sustained virologic efficacy. CDEC agreed with the clinical expert.</p>
Considerations for prescribing of therapy	
<p>Is access to infection disease specialists a concern to jurisdictions? Could a patient followed by their physician or nurse practitioner have this medication prescribed to them?</p>	<p>Patients could be followed by their physician or nurse practitioner if they are trained to recognize and manage treatment.</p> <p>Jurisdictional issues are a concern, but most patients with HIV live near large centres with access to care.</p> <p>Care is always initiated by, or in conjunction with, an HIV specialist, but could be managed in a community care setting.</p> <p>CDEC agreed with the clinical expert, noting that in some communities, there are cohorts of family doctors who are experts in primary care HIV, and who are very comfortable with ARVs.</p>

ARV = antiretroviral; CDEC = CADTH Canadian Drug Expert Committee; HIV-1 = HIV type 1; HTE = heavily treatment experienced; MDR = multidrug resistant; RNA = ribonucleic acid.

## Clinical Evidence

### Pivotal Studies and Protocol Selected Studies

#### Description of Studies

The BRIGHT study consisted of an initial DB phase that lasted 8 days, and a subsequent OL phase that remains ongoing through 240 weeks. In the DB phase, 272 patients with HIV-1 who were eligible to receive at least 1 fully active, approved ARV in 1 or 2 ARV classes at baseline were randomized, 3:1, to fostemsavir 600 mg twice daily or placebo, plus their baseline ARV regimen, for 8 days. The primary analysis was conducted after 8 days, and consisted of the primary outcome, the mean change from baseline to week 8 in HIV-1 RNA. Secondary outcomes, none of which were formally assessed, included the percentage of patients with a decrease in HIV-1 RNA of greater than 0.5 log<sub>10</sub> copies/mL and > 1.0 log<sub>10</sub> copies/mL at day 8, while in the OL phase, virologic response (HIV-1 RNA level of < 40 copies/mL at week 24, 48, and 96), resistance



testing for patients experiencing virologic failure, mean change in CD4+ count through week 96, and events resulting in a diagnosis of AIDS (using the Centers for Disease Control and Prevention classification system) were assessed. In addition to this randomized cohort, there was a nonrandomized cohort that consisted of patients who had no other options for fully active and approved ARV, and these patients received fostemsavir plus OBT, determined based on resistance testing and treatment history. In the randomized cohort, after day 8 patients entered an OL phase where they all received fostemsavir plus OBT. The study was expected to last at least 96 weeks, and will continue until an additional option, a rollover study, or marketing approval is in place.

Patients in the randomized cohort were approximately 48 years of age, and the majority were male (74% of patients) and white (68% of patients). Most patients (89% of patients) had a baseline viral load of 1,000 copies/mL or higher and [REDACTED] of patients had a baseline viral load of 30,000 copies/mL or more. Approximately one-quarter of patients had a CD4+ count of fewer than 20 cells/mm<sup>3</sup> and a similar percentage had a baseline CD4+ of 200 cells/mm<sup>3</sup> or more. Approximately one-third of patients had been treated for HIV for more than 20 years, and 85% of patients had a positive AIDS history, meaning that they either had a nadir CD4+ count of fewer than 200 cells/mm<sup>3</sup> or a response of “yes” to the question “Does participant have AIDS?” on the disease history component of the case report form. Most patients (90% or more) had prior exposure to a nonnucleoside reverse transcriptase inhibitor, nucleoside reverse transcriptase inhibitor, or protease inhibitor, while 75% had prior exposure to an integrase strand transfer inhibitor. Other ARVs that patients had prior exposure to included entry inhibitors (39%), CCR5 antagonists (26%), and [REDACTED]. The most common ARV classes in the failing regimen were nucleoside reverse transcriptase inhibitor (81%), protease inhibitor (67%), integrase strand transfer inhibitor (44%), and nonnucleoside reverse transcriptase inhibitor (28%), while other classes included CCR5 antagonists (12%) and entry inhibitors (4%).

### **Efficacy Results**

During the OL phase, after 96 weeks, 4% of patients died in the randomized cohort and 17% of patients died in the nonrandomized cohort. Overall, 2% of patients had a cause of death that was considered to be related to AIDS. The definition of an AIDS-related death was not provided; however, the identification of AIDS-related events, in general, in the BRIGHT trial was based on the Centers for Disease Control and Prevention list of AIDS-defining events. After 240 weeks, 6% of patients in the randomized cohort and 20% of patients in the nonrandomized cohort died, and [REDACTED] of patients overall had a cause of death related to AIDS. Patients with HIV who are HTE and physicians both highlighted the high risk of mortality in this population.

The percentage of patients progressing to AIDS was not specifically reported in the BRIGHT trial; however, patients with AIDS-related events was reported. In the DB phase, after 8 days there were 2 patients in the fostemsavir group who had an AIDS-related event (grade 3 serious adverse event [SAE] of recurrent pneumonia; grade 2 AE of herpes simplex virus, gastrointestinal, other than mouth, throat, perirectal) and 1 patient in the placebo group (grade 3 SAE of Candida esophagitis). After 96 weeks in the OL phase, [REDACTED] of patients who were originally assigned to the fostemsavir group and [REDACTED] of patients who were originally assigned to the placebo group had an AIDS-related event. In the nonrandomized cohort, [REDACTED]



had an AIDS-related event. [redacted] of patients originally assigned to the fostemsavir group and [redacted] originally assigned to the placebo group had an AIDS-related event, while [redacted] of patients in the nonrandomized cohort had an AIDS-related event. Patients with HIV who are HTE and physicians both highlighted the importance of reducing the risk of AIDS-related morbidities in this population. Hospitalizations were not reported in either the DB or OL phase, and this was an outcome from the CADTH systematic review protocol that would have provided further context into the impact of adding fostemsavir to OBT on important clinical outcomes in this population.

The mean change from baseline to day 8 in plasma HIV-1 RNA  $\log_{10}$  copies/mL was  $-0.791 \log_{10}$  copies/mL (95% CI,  $-0.885$  to  $-0.698$ ) in the fostemsavir group and  $-0.166 \log_{10}$  copies/mL (95% CI,  $-0.326$  to  $-0.007$ ) in the placebo group, for a difference between groups of  $-0.625 \log_{10}$  copies/mL (95% CI,  $-0.810$  to  $-0.441$ ;  $P < 0.0001$ ). There were [redacted] of fostemsavir patients and [redacted] of placebo patients who achieved a decrease in HIV-1 RNA of more than  $0.5 \log_{10}$  copies/mL by day 8 and [redacted] of fostemsavir patients and [redacted] of placebo patients who achieved a decrease in HIV-1 RNA of more than  $1.0 \log_{10}$  copies/mL by day 8. In the OL phase, the percentage of patients with HIV-1 RNA of less than 40 copies/mL remained consistent from week 24 (56%) to week 48 (57%) to week 96 (61%) and levelled off at week 240.

[redacted] For patients with [redacted], there was a mean [redacted] with fostemsavir and with placebo; and for patients with baseline [redacted] there was a mean [redacted] with fostemsavir and [redacted] with placebo. Subgroup data for [redacted] was also reported. Patients with a baseline [redacted] with fostemsavir and with placebo, while patients with a baseline [redacted] in the fostemsavir group and [redacted] in the placebo group. For patients with a baseline [redacted], the mean change from [redacted] with fostemsavir and [redacted] with placebo, and for patients with a baseline [redacted], the adjusted mean change from baseline to day 8 was with fostemsavir and [redacted] with placebo. Finally, in patients with a baseline [redacted], the adjusted mean change [redacted] with fostemsavir and [redacted] in the placebo group.

At day 8, the mean change from day 1 in CD4+ counts was [redacted] in the fostemsavir group from a baseline of [redacted] and [redacted] in the placebo group from a baseline of [redacted]. In the OL phase, the mean change from baseline to week 96 in CD4+ counts was [redacted] in the randomized cohort and [redacted] in the nonrandomized cohort. After 240 weeks, the mean change from baseline in CD4+ counts was 296.4 cells/mm<sup>3</sup> (SD = 227.5) in the randomized cohort and 240.0 cells/mm<sup>3</sup> (318.5) in the nonrandomized cohort.

[redacted]  
[redacted]  
[redacted]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The mean Functional Assessment of HIV Infection (FAHI) total score increased (improved) from baseline to week 96 in both cohorts, by 5.3 points (SD = 24.0) in the randomized cohort and by 4.9 points (26.4) in the nonrandomized cohort.

### Harms Results

In the OL phase, after 96 weeks, 92% of patients in the randomized cohort and 99% of patients in the nonrandomized cohort experienced an AE. After 240 weeks, 95% of patients in the randomized cohort and 99% of patients in the nonrandomized cohort experienced an AE. The most common AEs occurring after 96 weeks, in both the randomized and nonrandomized cohorts, were diarrhea ([REDACTED]), nausea ([REDACTED]), and upper respiratory tract infection ([REDACTED]). [REDACTED]

[REDACTED]

In the 8-day DB phase, 2% of patients in the fostemsavir group and 3% of patients in the placebo group experienced an SAE. The only SAE that occurred in more than 1 patient in either group was pneumonia, which occurred in 2 patients (< 1%) in the fostemsavir group and none in the placebo group. During the OL phase, after 96 weeks, 34% of patients in the randomized cohort and 48% of patients in the nonrandomized cohort experienced an SAE, while after 240 weeks, 45% of patients in the randomized cohort and 56% of patients in the nonrandomized cohort had experienced an SAE. The most common SAE was pneumonia, occurring in 4% of patients in the randomized cohort and 3% of patients in the nonrandomized cohort after 96 weeks, and after 240 weeks, 8% of patients in the randomized cohort and 4% of patients in the nonrandomized cohort. In the OL phase, after 96 weeks there were 5% of patients in the randomized cohort and 12% of patients in the nonrandomized cohort, and after 240 weeks there were 6% of patients in the randomized cohort and 13% of patients in the nonrandomized cohort who discontinued treatment due to an AE. The most common reason was “infections and infestations,” occurring in 2% of patients in the randomized cohort after 96 and after 240 weeks and 5% of patients after 96 weeks and 6% of patients after 240 weeks in the nonrandomized cohort. Notable harms were infrequent during the DB phase, with the following events occurring in less than 1% of patients treated with fostemsavir: immune reconstitution inflammatory syndrome, corrected QT (QTc) prolongation, and increased blood alkaline phosphatase. After 96 weeks in the OL phase, immune reconstitution inflammatory syndrome had occurred in 2% of patients, and this was unchanged at the 240 week follow-up. QTc prolongation had occurred in 4% of patients after 96 weeks, and the percentage of patients experiencing QTc prolongation was not reported for the 240 week follow-up. There were 1% of patients who reported alanine transaminase of more than 3 times the upper limit of normal and total bilirubin of more than 2 times the upper limit of normal after 96 weeks and after 240 weeks.

## Critical Appraisal

With respect to internal validity, the BRIGHTHE study appeared to be reasonably well-conducted with respect to measures taken to ensure adequate blinding during the 8-day DB period, and to maintain allocation concealment during randomization. Assessment of health-related quality of life, an important outcome for the HTE population, was subject to considerable bias due to lack of blinding during the OL period, and the data are difficult to place into context due to a lack of control group. The FDA snapshot analysis was used to report results for virologic response. This is a conservative approach that counts missing samples as failures, and may have confounded the results as attrition increased from week 96 to week 240. The use of OBT in the OL phase means that the background therapy that patients received, in addition to fostemsavir, was not standardized, and it assumes that all patients were indeed optimized for their specific clinical situation. Disposition for the 8-day DB phase was not reported in the Clinical Study Report; therefore, it is not known whether there was a difference in withdrawals between the fostemsavir and placebo groups for this phase, which could potentially impact interpretation of efficacy and harms.

With respect to external validity, although the 8-day DB phase followed FDA guidance for assessing ARV, this short duration of follow-up limited the ability to assess any outcomes outside of viral load. For example, CD4+ counts typically take several months to increase in response to a reduction in viral load, and one would not expect to see differences in risk of AIDS-related deaths or progression to AIDS in 8 days. The HTE population is at much higher risk of experiencing AIDS-related complications such as opportunistic infections and death; therefore, there remains a gap in knowledge regarding the impact of fostemsavir on these important outcomes in these patients.

## Indirect Comparisons

The BRIGHTHE trial included an 8-day randomized phase that compared fostemsavir plus OBT to placebo plus OBT, followed by a single-arm phase wherein all patients received fostemsavir plus OBT. Indirect comparisons were therefore required to estimate comparative effectiveness for any outcomes beyond 8 days.

## Description of Studies

The sponsor submitted 1 matching-adjusted indirect comparison (MAIC) and CADTH identified 1 published MAIC.

The objective of the sponsor-submitted MAIC was to generate long-term comparative efficacy estimates for fostemsavir plus OBT versus OBT alone for the management of patients with HIV who are HTE using individual patient data from the BRIGHTHE study. The data for OBT alone was populated using outcomes from the VIKING-3 study, which was identified through a systematic literature review and assessed to be the most closely aligned with the BRIGHTHE trial in terms of patient eligibility criteria regarding treatment history, resistance status, and available treatments remaining. The VIKING-3 study was also identified as the most relevant for the context of Canadian treatment practices and patients in Canada based on a sponsor-conducted feasibility assessment and consultation with physicians.

The published MAIC included the same analysis submitted by the sponsor, alongside analyses comparing the BRIGHTE trial to the TMB-301 and BENCHMRK trials, which were considered to be less relevant for the purpose of this review. The TMB-301 study evaluated ibalizumab, which is not currently available or marketed for use in Canada; additionally, nearly half of the patients in the TMB-301 trial used fostemsavir in their OBT, and subgroup data were not available to exclude these patients. The BENCHMRK study began in 2006, and the ARV regimens used in the OBT alone group did not closely reflect the combination of regimens used in the BRIGHTE study or in current Canadian practice (most notably lacking was dolutegravir).

In the sponsor-submitted MAIC comparing the BRIGHTE trial to the VIKING-3 trial as a representation of OBT alone, efficacy was assessed in terms of:

- change (from baseline) in CD4+ cell count
- rates of virologic suppression
- rates of protocol-defined virologic failure (PDVF)
- rates of treatment discontinuation.

Secondary analyses included an assessment of the relative safety profile of fostemsavir based on the rates of SAEs, discontinuation due to AEs, and death.

### **Efficacy Results**

[Redacted content]

### **Harms Results**

The results of the safety-related MAICs (patients with any SAE, cellulitis, dehydration, pneumonia, pyrexia, acute kidney injury, death, and discontinuation due to AEs) were inconclusive due to wide 95% CIs that included the null value.

### **Critical Appraisal**

The VIKING-3<sup>6</sup> single-arm study of dolutegravir-containing regimens had the most comparable HTE HIV population and patients were treated with ARV regimens that were the most closely reflective of those in the BRIGHTE trial and Canadian clinical practice; these primarily includes dolutegravir, darunavir, and tenofovir disoproxil fumarate-emtricitabine. Because 82% of patients in the BRIGHTE trial received dolutegravir as part of their OBT, the VIKING-3 study was an appropriate trial to select as a comparator.

Although adjustments conducted for the MAICs were generally appropriate and the sponsor followed a comprehensive and expert-guided process to identify prognostic factors and treatment effect modifiers, it is unknown whether all relevant variables were captured. Unanchored MAICs require very strong assumptions about the data and require that all known and unknown prognostic factors and treatment effect modifiers are accounted for. This may be particularly difficult to meet for discontinuation and safety-related outcomes.

The distribution of overall susceptibility score<sub>new</sub> in the VIKING-3 study at baseline had to be recalculated to account for patient exposure to dolutegravir throughout the trial. Although multiple assumptions were explored, it is unknown which assumption is the most appropriate and the magnitude and direction of potential bias is uncertain.

In adjusting the population of the BRIGHTE trial to match the population of the VIKING-3 trial for MAIC, there was a drop in sample size of nearly 80%, reflecting poor overlap between the trials. The BRIGHTE study allowed patients with no fully active ARVs remaining (in the nonrandomized cohort), whereas the VIKING-3 study required at least 1. The adjusted population primarily represents participants in the BRIGHTE trial with more treatment options remaining (i.e., to reflect the distribution of overall susceptibility score<sub>new</sub> in the VIKING-3 trial) and is therefore not representative of the full population eligible for fostemsavir, especially those with highly resistant disease and no fully active ARVs remaining.

Although there were statistically significant results for the MAICs of discontinuation and PDVF, interpretation is compromised by the limitations of unanchored MAICs, substantial sample size reduction, and differences in the definition of PDVF between the trials.

The results for change in CD4+ cell count and proportion with virologic suppression (HIV-1 RNA < 50 copies/mL) were inconclusive due to CIs that included the null value.

The results for safety outcomes were generally imprecise and the interpretation is compromised by substantial differences in study drug exposure in both the primary analysis (comparing the 48-week data cut-off of each trial) and the sensitivity analysis (a 24-week data cut-off in the BRIGHTE trial compared to a 48-week data cut-off of in the VIKING-3 trial).

Overall, the MAICs were determined to be inconclusive due to the limitations of the available evidence.

### Other Relevant Evidence

There were no extensions and no other relevant studies in the population of interest identified for this review.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population(s)	Adult patients with multidrug-resistant HIV for whom it is otherwise not possible to construct a suppressive antiviral regimen (as per indication)
Treatment	Fostemsavir
Dose regimen	600 mg taken orally twice daily
Submitted price	\$62.77 per 600 mg tablet
Treatment cost	\$45,822 annually per patient
Comparators	OBT defined as an average mix of the most commonly used regimens, based on a mix of treatments available in the BRIGHTE randomized trial cohort (including NRTIs, NNRTIs, FIs, PIs, and INSTIs)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (53 years)
Key data source	<ul style="list-style-type: none"> <li>Short-term (8 days) comparative efficacy between fostemsavir and placebo from the BRIGHTE trial</li> <li>Long-term comparative efficacy of fostemsavir plus OBT vs. OBT alone from a MAIC to the VIKING-3 study population</li> </ul>
Key limitations	<ul style="list-style-type: none"> <li>The comparative clinical effectiveness of adding fostemsavir to OBT is uncertain due to the short observation period of the BRIGHTE trial (8 days). Additionally, long-term comparative effects were estimated through a MAIC with methodological limitations that make the magnitude of benefit of fostemsavir highly uncertain.</li> <li>The method used to model the natural history of patients with HIV based on CD4+ count lacked transparency and could not be validated. This added additional uncertainty to the estimated long-term clinical effectiveness estimates.</li> <li>Nearly all incremental QALYs were estimated through extrapolation, but no evidence was available to quantify the durability of fostemsavir's effect on CD4+ count over time.</li> <li>The sponsor's pharmacoeconomic model assumed that CD4+ count and viral load were independent, with equal transition probabilities between CD4+-based health states irrespective of viral load. This assumption was not supported by evidence or clinical expertise.</li> <li>Uncertainty around multiple inputs in the model was based on arbitrary values rather than evidence from the trial, the MAIC, or the literature. Consequently, the uncertainty has not been effectively captured in the model.</li> <li>Parameter uncertainty within the model appears to introduce an asymmetric bias in estimated costs and QALYs. This asymmetry creates a notable discrepancy between deterministic and probabilistic results that favoured OBT alone.</li> </ul>
CADTH reanalysis results	<ul style="list-style-type: none"> <li>Given the limitations identified within the sponsor's economic analysis, CADTH was not able to use the model to provide a more reliable estimate of the cost-effectiveness of fostemsavir. The sponsor's submitted results produced an ICER of \$469,086 per QALY gained (incremental cost = \$315,607; incremental QALYs = 0.673)</li> <li>Based on the sponsor's analysis, a 94% price reduction would be required for fostemsavir plus OBT to be</li> </ul>

Component	Description
	considered cost-effective at a WTP threshold of \$50,000 per QALY gained compared to OBT alone. Even with this price reduction, the probabilistic results suggest a 36% probability that fostemsavir would not be cost-effective at any WTP threshold, due to high uncertainty around the predicted QALYs.

FI = fusion inhibitor; ICER = incremental cost-effectiveness ratio; INSTI = integrase strand transfer inhibitor; LY = life-year; MAIC = matching-adjusted indirect comparison; NNRTI = nonnucleoside reverse transcriptase inhibitors; NRTI = nucleotide reverse transcriptase inhibitors; OBT = optimized background therapy; PI = protease inhibitor; QALY = quality-adjusted life-year; vs. = versus; WTP = willingness to pay.

### Budget Impact

CADTH did not conduct a base-case analysis, as the sponsor’s submission provided adequate presentation of the budget impact for fostemsavir plus OBT. The sponsor’s base case suggested a 3-year budget impact of \$19,579,518.

## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

**Meeting date:** March 22, 2023

**Regrets:** One of the expert committee members did not attend.

**Conflicts of interest:** None