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## CADTH Reimbursement Recommendation

# Cabotegravir (Apretude)

**Indication:** For at-risk adults and adolescents aged 12 years and older and weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.

**Sponsor:** ViiV Healthcare ULC

**Final recommendation:** Reimburse with conditions

# Summary

## What Is the CADTH Reimbursement Recommendation for Apretude?

CADTH recommends that Apretude should be reimbursed by public drug plans for at-risk adults and adolescents aged 12 years and older and weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection, if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Apretude should only be covered by public drug plans in a similar manner to tenofovir disoproxil fumarate–emtricitabine (TDF-FTC) for of HIV-1 PrEP.

### What Are the Conditions for Reimbursement?

Apretude should only be reimbursed if there is a reduction in price and if the economic feasibility of the adoption of Apretude is addressed.

### Why Did CADTH Make This Recommendation?

- Evidence from 2 randomized controlled trials demonstrated that treatment with Apretude reduced the incidence of HIV-1 infections in people who were vulnerable to sexually acquiring HIV-1 compared to treatment with oral TDF-FTC.
- Apretude appears to meet some needs identified by patients as an effective PrEP option that is well tolerated and provides an intramuscular drug option with reduced treatment intervals. The dosing frequency for Apretude may help some patients adhere to treatment; however, a conclusion could not be drawn based on the available evidence.
- Based on public list prices, Apretude is estimated to cost the public drug plans approximately $73,000,000 over the next 3 years. However, the actual budget impact is uncertain because the methods used to calculate the market size were identified as a limitation to the submitted analysis.

## Additional Information

### What Is HIV-1?

The human immunodeficiency virus (HIV) is a retrovirus that attacks and damages cells within the human immune system. It is transmitted through bodily fluids, which can occur by having sex with someone living with HIV or by vertical transmission during pregnancy, childbirth, and/or breastfeeding. Without treatment, HIV can weaken the immune system, leading to AIDS. HIV-1 is a subtype of HIV responsible commonly reported in Canada. People living with HIV are more prone to other infections and

# Summary

diseases that can eventually cause death. In 2022, there were 1,833 new HIV diagnoses in Canada (6.3 per 100,000 new infections in males and 3.1 per 100,000 in females [excluding trans individuals or if sex was not reported]). These estimates represent a 4.7 incidence per 100,000 of the population.

### Unmet Needs in HIV-1

The effectiveness of PrEP depends on key behavioural factors that impact efficacy, such as medication adherence and successful patient participation in routine clinical follow-up. Although there are currently 2 oral PrEP options in Canada, TDF-FTC and tenofovir alafenamide fumarate–emtricitabine, there is stigma and adherence challenges associated with current options for high-incidence populations. Thus, there is a need for options that are convenient to individuals and promote adherence.

### How Much Does Apretude Cost?

With an oral lead-in, treatment with Apretude is expected to cost $11,252 per patient in the first year of treatment and $10,260 per patient in every subsequent year. Without an oral lead-in, Apretude is expected to cost $10,260 per patient per year.

## Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that cabotegravir be reimbursed for at-risk adults and adolescents aged 12 years and older and weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

The interim analyses of 2 pivotal multicentre, double-blind randomized controlled trials (RCTs), HPTN 083 and HPTN 084, suggests that long-acting cabotegravir (cabotegravir LA) reduces the incidence of HIV-1 in people who are at risk of sexually acquiring HIV-1 compared to treatment with oral tenofovir disoproxil fumarate–emtricitabine (TDF-FTC). HPTN 083 is an ongoing phase IIb/III noninferiority RCT that included cisgender men who have sex with men and transgender women who have sex with men (gbMSM) at risk of sexually acquired HIV-1. This study demonstrated that treatment with cabotegravir LA was noninferior to TDF-FTC based on a reduction in the risk of incident HIV-1 infection of 66% (hazard ratio [HR] = 0.34; 95% confidence interval [CI], 0.18 to 0.62; P = 0.0005) after 6,404 person-years of accumulated follow-up. HPTN 084 is an ongoing phase III superiority trial of cisgender women at increased risk of sexually acquiring HIV-1. This study demonstrated an 88% (HR = 0.12; 95% CI, 0.05 to 0.31; P ≤ 0.0001) reduction in risk of incident HIV-1 infection after 3,907 person-years of accumulated follow-up. An assessment of incident HIV-1 diagnoses during step 2 of the trials only (excluding the oral cabotegravir lead-in [step 1]) demonstrated noninferiority to TDF-FTC based on a 79% reduction in the incidence of HIV-1 infections in HPTN 083, and superiority to TDF-FTC based on a 94% reduction in the incidence of HIV-1 infections in HPTN 084. Regarding the safety profile of cabotegravir LA, injection site reactions were the most reported adverse event observed in both trials, although considered manageable in clinical practice, with no new safety signals identified.

CDEC noted that although there are PrEP options currently available in Canada (i.e., TDF-FTC and emtricitabine–tenofovir alafenamide fumarate [FTC-TAF]), these oral regimens may not benefit all at-risk populations. Input from patient groups indicated that patients expressed a need for effective treatments that improve adherence, are well tolerated, and can improve quality of life. CDEC concluded that cabotegravir LA is an effective option with a manageable tolerability profile and reduced dosing frequency, although a conclusion regarding an improvement in adherence and quality of life could not be drawn based on the available evidence.

Using the sponsor-submitted price for cabotegravir and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for cabotegravir was $29,283 per quality-adjusted life-year (QALY) compared with TDF-FTC. At this ICER, cabotegravir is cost-effective at a $50,000 per QALY willingness-to-pay threshold for adults (gbMSM and cisgender women) who weigh at least 35 kg and are at increased risk of acquiring HIV-1 infection.

### Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation, renewal, discontinuation, and prescribing** | | |
| 1. Criteria for reimbursement of cabotegravir LA should be based on the criteria used by each of the public drug plans for initiation, renewal, discontinuation, and prescribing of TDF-FTC for HIV-1 PrEP. | There is insufficient evidence to suggest that cabotegravir LA should be held to a different standard than other options currently reimbursed for HIV-1 PrEP. | — |
| **Pricing** | | |
| 2. A reduction in price. | At publicly available list prices for all comparators, cabotegravir LA was associated with an ICER of $29,283 per QALY gained compared to oral PrEP. At this ICER, no price reduction is needed to achieve cost-effectiveness at a willingness-to-pay threshold of $50,000 per QALY gained.<br>The ICER is sensitive to assumptions about drug cost and patient adherence. A price reduction may be required to achieve cost-effectiveness if the assumptions in the CADTH base case are not met. | — |
| **Feasibility of adoption** | | |
| 3. The economic feasibility of adoption of cabotegravir must be addressed. | At the submitted price, the total drug plan expenditure for cabotegravir is expected to be greater than $40,000,000 in year 3. | — |

FTC = emtricitabine; ICER = incremental cost-effectiveness ratio; LA = long acting; PrEP = pre-exposure prophylaxis; QALY = quality-adjusted life-year; TDF = tenofovir disoproxil fumarate.

## Discussion Points

- CDEC discussed the certainty of evidence for the treatment benefit of cabotegravir LA compared to TDF-FTC, which was rated as high in both trials. This was true for both the combined oral lead-in and injection phases (step 1 and step 2), and injection phase only (step 2 only). However, in the absence of an evidence-based clinically meaningful threshold, the clinical importance of the observed between-group difference is less certain.
- CDEC discussed the importance of adherence for efficacy of PrEP options and the evidence available in the review. Although differences in adherence in favour of cabotegravir LA were observed in the trials, definitive conclusions could not be drawn to support a correlation between adherence and cabotegravir LA benefit for the primary efficacy outcome due to several limitations. A key limitation is that adherence analyses were conducted in a sample of each treatment group in both trials, which may not represent the entire population enrolled. Further, the small sample size may overestimate the treatment effect. Also, as noted by the clinical expert, adherence measured using pharmacokinetic

measurements of drug levels may not truly represent adherence (especially for oral TDF-FTC) due to existing biological variability in drug metabolism between individuals across populations. Adherence observed in clinical trials may also not reflect what is observed in clinical practice.

- CDEC noted that direct or indirect evidence comparing cabotegravir LA to FTC-TAF was not available for this review and therefore the relative efficacy and safety is unknown. The network meta-analysis (NMA) that was included in the submission provided evidence of comparative effectiveness of cabotegravir LA to no PrEP in reducing HIV-1 infections; however, there is uncertainty in the NMA findings due to several limitations preventing the assessment of key assumptions of the analyses.
- The duration of follow-up in both trials was considered appropriate and long enough to identify HIV events for the population enrolled; however, evidence of long-term safety and efficacy beyond the pivotal trials was not available for this review.
- CDEC noted that data on adolescent populations were limited. This is further discussed within Table 2 under Considerations for Initiation of Therapy.
- CDEC noted that the relative cost-effectiveness of cabotegravir LA compared to oral PrEP was highly sensitive to assumptions about patient adherence. If patients have higher adherence to cabotegravir LA than oral PrEP, the cost-effectiveness of cabotegravir LA becomes more favourable. Conversely, if patients prefer oral PrEP, cabotegravir LA becomes less cost-effective. Additionally, the ICER estimated by CADTH was based on publicly available list prices for all comparators including oral PrEP. The available evidence for treatment adherence between these 2 approaches is uncertain, and the negotiated price of oral PrEP may be lower than the publicly available listed price. A reduction in the price of cabotegravir LA may be required to achieve cost-effectiveness compared to oral PrEP.

## Background

HIV is a retrovirus that impairs the human immune system, and is transmitted via sex, blood, or vertically (i.e., during pregnancy, childbirth, and/or breastfeeding). Without treatment, HIV can progress from acute through clinical latency to AIDS, making people living with HIV more vulnerable to opportunistic infections and diseases. At the end of 2020, there were 62,790 (range, 55,200 to 70,300) people in Canada living with HIV. The prevalence rate was approximately 170 per 100,000 persons, representing a 3.6% increase from the estimated 60,600 people living with HIV reported at the end of 2018. In 2022, there were 1,833 new HIV infections were diagnosed in Canada, representing a 4.7 incidence per 100,000, and a 24.9% increase from estimates reported in 2021 according to the Public Health Agency of Canada (PHAC). The estimated rate of new HIV infections in males was 6.3 per 100,000 and 3.1 per 100,000 females (excluding trans individuals or if sex was not reported).

Canada has adopted an integrated approach toward HIV management and prevention. PrEP, which involves the use of antiretroviral drugs to prevent HIV infection, is an effective tool when used in combination with other strategies in the prevention of HIV for high-incidence populations. However, the effectiveness of any PrEP option depends on key behavioural factors that affect efficacy, such as medication adherence and

participation in clinical follow-up. There are currently 2 PrEP options in Canada: TDF-FTC and FTC-TAF. TDF-FTC is an oral therapy that is reimbursed by most jurisdictions in Canada, whereas FTC-TAF is not indicated for individuals at risk from receptive vaginal sex and is only reimbursed through the Canadian Armed Forces Drug Benefit List. Although PrEP usage in Canada has increased over the past years, it is most commonly used by gbMSM, driven by education and awareness initiatives for the use of PrEP. Almost all (98%) PrEP users in Canada were male. There is a need for options that are convenient to individuals and that promote adherence according to the clinical expert consulted during the review.

Cabotegravir is an antiretroviral medication, which inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Cabotegravir has been approved by Health Canada for at-risk adults and adolescents aged 12 years and older and weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection. Cabotegravir is available as 30 mg oral tablets and 200 mg/mL (600 mg/3 mL) extended-release injectable solution. The recommended dose depends on whether an oral lead-in option is selected initially or the cabotegravir LA injection is initiated directly. When an oral lead-in regimen is selected, the recommended dose is as a 30 mg oral lead-in cabotegravir tablet once daily (for at least 28 days), followed by intramuscular initiation injections of 3 mL (600 mg) cabotegravir LA at month 1 and month 2 (month 1 is administered on the last day of oral lead-in or within 3 days thereafter), then intramuscular continuation injections with 3 mL (600 mg) cabotegravir LA from month 4 and every 2 months onward. When the cabotegravir LA injection is initiated directly, the recommended dose is an intramuscular initiation injection of 3 mL (600 mg) at month 1 and month 2, followed by intramuscular continuation injections of 3 mL (600 mg) at month 4 and every 2 months onward.

Cabotegravir LA monotherapy has not previously undergone a reimbursement review for PrEP for HIV-1 prevention. However, cabotegravir (tablets and injectable forms) in combination with rilpivirine has been previously reviewed for the treatment of HIV-1 in patients living with HIV-1.

## Sources of Information Used by the Committee

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

- a review of 2 RCTs (1 phase IIb/III, randomized, multicentre, double-blind, double-dummy, noninferiority study in gbMSM and TGW and 1 phase III, randomized, multicentre, double-blind, double-dummy, open-label, superiority study conducted in cisgender women) in adults at higher risk of acquiring HIV-1; 2 single-arm, noncomparative studies conducted in adolescents at higher risk of acquiring HIV-1; and 1 indirect treatment comparison
- patients' perspectives gathered by 5 patient groups (Africans in Partnership Against AIDS [APAA], HIV Network of Edmonton Society [HIV Edmonton], CATIE, Community-Based Research Centre [CBRC], and Peer Outreach Support Services and Education [POSSE])
- input from public drug plans that participate in the reimbursement review process

- 1 clinical specialist with expertise diagnosing and treating patients at risk for acquiring and living with HIV
- input from 2 clinician groups (Vancouver Coastal Health [VCH] and 1 clinician from the Division of Infectious Diseases in the Faculty of Health Sciences at McMaster University)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

Five patient groups submitted inputs on the indication being reviewed: APAA, HIV Edmonton, CATIE, CBRC, and POSSE.

All patient groups highlighted the stigma related to HIV and discrimination at the system level, in the laws and institutions, within the medical profession and communities at large, and between individuals or by oneself in the form of shame and guilt. The stigma often leads to isolation and fear of disclosure that can affect treatment maintenance or medication drop off and the quality of life of those affected by HIV. According to the Sex Now 2021 online survey, the awareness of PrEP for HIV as a medication to prevent HIV varies among high-incidence populations. Patients from 2 groups (APAA and CATIE) identified racism and cultural and linguistic barriers as deterrents for "African Caribbean Black people" [from original source] living with HIV from accessing treatment. Other identified barriers included homophobia, limited information and access to health care facilities, and financial constraints. Other groups highlighted challenges such as side effects of oral medications on the digestive and intestinal systems, pill burden, and the impact of daily medication on lifestyle can affect treatment adherence. One input noted that youth struggle with adherence to medications and require solutions reducing adherence requirements.

Patient groups highlighted that there are stigma and adherence issues associated with current oral PrEP options (i.e., Truvada and Descovy). The patient groups noted that remembering to take oral pills is a challenge when they are using drugs or dealing with competing priorities. The groups highlighted concerns relating to the safety of storing medications, especially for persons in need of shelter, and the ongoing need to continually seeking renewal of prescriptions.

Patients expressed their preference for injectable PrEPs according to 1 survey (Sex Now 2022). The advantages of injectable PrEPs identified by patients include the reduced stigma experienced in multiple settings due to reduced exposure to health services or systems in which stigmatizing experiences occur, increased privacy and discretion, decreased risk of treatment interruptions when they travel, increased adherence to treatment, reduced impact on digestive-related issues from consuming pills, and improved quality of life (e.g., improved autonomy and self-determination such as having a choice in treatment decisions, and the sense of living of life that is not encumbered by medication regimens).

Patients expect new PrEP therapies to demonstrate improved access to treatment, improved treatment adherence, decreased breakthrough infections, decreased risk of resistance, sustained viral suppression, and increased level of comfort in the treatment.

## Clinician Input

### Input From Clinical Experts Consulted for This Review

The clinical expert consulted during the review highlighted that an important goal in the management of HIV in Canada is to prevent persons from acquiring HIV infections sexually using different strategies. The expert noted that PrEP is an important tool available to persons at increased risk of acquiring HIV for the prevention of HIV-1 infections; however, current options (including oral therapies TDF-FTC [Truvada] and FTC-TAF [Descovy]) do not cater to all populations. Therefore, there is an unmet need for newer treatments that are convenient and promote adherence in all high-incidence populations. The clinical expert anticipates that cabotegravir LA injectable would provide an alternative to daily oral treatment for individuals hoping to access PrEP options. According to the clinical expert, all persons considered at risk of acquiring HIV sexually will benefit from cabotegravir LA as a PrEP option. The expert noted that cabotegravir LA will be less suitable for individuals who cannot tolerate injections. The expert indicated that response to treatment will be assessed based on whether persons remain HIV-negative during routine follow-up tests, which are typically performed every 3 to 6 months. The expert highlighted that factors such as individual intolerance to treatment and the acquisition of HIV will lead to treatment discontinuation. Although injection reactions are frequently observed, the expert noted that patients usually tolerate these adverse events; however, a severe injection site reaction (ISR) may precipitate changes in treatment modality. The clinical expert highlighted cabotegravir LA can be prescribed by any clinician who provides PrEP care and follow-up (these include sexual health clinics, physicians, primary care providers, or infectious diseases specialists).

### Clinician Group Input

Two inputs were submitted on the indication being reviewed: 1 clinician group of 6 clinicians, VCH Regional HIV Program, which is a public health program that aims to reduce the rate of HIV infection among the 1.25 million people living in the region, and 1 clinician, Dr. Philippe El-Helou.

Inputs from clinician groups are in line with the clinical expert consulted for this review regarding oral PrEPs that are currently available for individuals who are at higher risk of acquiring HIV, the treatment goal is to decrease the incidence of newly acquired HIV infections, and there remains an unmet need to improve treatment compliance and convenience. Both the clinical expert consulted for this review and the clinician groups agreed that cabotegravir LA would be an alternative to daily oral PrEP and the patients best suited for cabotegravir LA would be individuals who are at risk of sexually acquired HIV. Clinicians from VCH Regional HIV Program specified that individuals in whom adherence to oral daily HIV PrEP is difficult are best suited to long-acting injectable HIV PrEP. The clinical expert consulted for this review aligns with the clinician groups in using incident HIV infections as an outcome to determine patients' response to treatment in clinical practice. Inputs from clinician groups highlighted that oral PrEP along with robust monitoring and follow-up strategy are crucial. Clinician groups stated that cabotegravir LA should be prescribed and monitored by various health care providers (e.g., family doctors, nurse practitioners, and specialists in HIV care) in

community, hospital, and specialty clinics where individuals can access PrEP prescriptions, HIV testing, and ongoing care.

## Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for cabotegravir:

- relevant comparators
- considerations for initiation of therapy
- consideration for prescribing of therapy
- generalizability
- system and economic issues.

The clinical expert consulted for this review provided advice on the potential implementation issues raised by the drug programs.

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

| Implementation issues | Response |
|---|---|
| **Relevant comparators** | |
| There are 2 PrEP modalities available in Canada: TDF-FTC (Truvada) and FTC-TAF (Descovy).<br>Both clinical trials (HPTN 083 and HPTN 084) used TDF-FTC as the comparator, which is the therapy reimbursed by the federal, provincial, and territorial jurisdictions. FTC-TAF is only funded in 1 Canadian jurisdiction. | This is a comment from the drug plans to inform CDEC deliberations. |
| **Considerations for initiation of therapy** | |
| Clinical trials included participants who were at high risk for HIV acquisition.<br>How should high risk be defined (i.e., use Canadian PrEP guidelines definition?) | The clinical expert considered the definition of high risk for individuals in the Canadian guidelines on PrEP as appropriate to be used in clinical practice.<br>According to the guidelines, the definition of *high risk* depends on the type of exposure (anal, vaginal, or oral sex, or percutaneous). The guidelines define exposures at higher risk for HIV transmission to include condomless receptive anal sex and needle sharing. Exposures conferring moderate risk include condomless insertive anal sex and vaginal sex.<br>CDEC notes that the definition of high risk according to the Canadian guidelines on PrEP differs from the criteria used in the pivotal trials (HPTN 083 and HPTN 084) and the reimbursement criteria of individual jurisdictions. |
| HPTN 083 was conducted in MSM and TGW aged 18 years or older without HIV and at high risk for HIV acquisition; HPTN 084 was conducted in cisgender women aged 18 to 45 years who were at high risk for HIV acquisition. | The clinical expert did not consider age as a determining factor for the use of cabotegravir LA because the patients included in the studies were eligible based on their body weight (weight above 35 kg). According to the expert, adolescent persons weighing 35 kg or more will be eligible to receive cabotegravir |

| Implementation issues | Response |
|---|---|
| Could this be considered for use in patients under 18 years of age? | LA if they are considered at risk for acquiring HIV-1 sexually.<br>CDEC also acknowledges that findings from a small subset study conducted in an adolescent population (HPTN 083-01 and HPTN 084-01) did not identify any new safety signals, although this study was limited by a small sample size and an open-label, single-arm design. Therefore, CDEC defers to the expertise of the clinical experts. |
| Cabotegravir tablets may be used as an oral lead-in to assess tolerability of cabotegravir before administration of cabotegravir LA injections or as short-term oral PrEP in individuals who will miss planned dosing with cabotegravir LA injections.<br>Should lead-in with cabotegravir oral tablets be required to assess tolerability before administration of cabotegravir LA injections? | The clinical expert consulted anticipates a variation in the use of the oral lead-in option for cabotegravir LA in practice. The expert noted that given the familiarity of clinicians to cabotegravir LA's safety profile (observed from its use in combination therapies for HIV-1 infections), an oral lead-in during initiation may not be required for all candidates. The expert noted that cabotegravir LA has a tolerable safety profile; therefore, health care professionals prescribing the drug for PrEP may recommend the oral lead-in tablets to individuals with concerns related to the intramuscular injection safety at initiation.<br>CDEC defers to the expertise of the clinical experts. |
| For consistency with initiation criteria associated with other drugs reviewed for reimbursement in the same therapeutic space consider aligning with criteria for TDF-FTC for PrEP. | This is a comment from the drug plans to inform CDEC deliberations. |
| **Considerations for prescribing of therapy** | |
| Should this be restricted to prescribers in the context of a sexual health program or by a specialist experienced in the diagnosis and management of HIV? | The clinical expert indicated that any health care professional who provides PrEP care and monitoring is eligible to prescribe and monitor the use of cabotegravir LA in practice. These would include sexual health clinics, physicians, primary care providers, or infectious diseases specialists. The expert noted that access to treatment is clinic specific and, although any prescriber could prescribe cabotegravir LA, intramuscular drug administration will typically be performed in clinics with trained personnel for intramuscular injections.<br>CDEC defers to the expertise of the clinical experts. |
| For consistency with prescribing criteria associated with other drugs reviewed for reimbursement in the same therapeutic space, consider aligning with criteria for TDF-FTC. | This is a comment from the drug plans to inform CDEC deliberations. |
| **Generalizability** | |
| Could pediatric patients and/or patients weighing less than 35 kg be considered eligible? | The clinical expert noted that pediatric patients weighing more than 35 kg who are considered at risk of acquiring HIV-1 infections sexually will be eligible to receive cabotegravir LA because the efficacy of the drug is weight dependent and not age dependent.<br>CDEC defers to the expertise of the clinical experts. |
| **System and economic issues** | |
| May have a significant budget impact.<br>For participating drug plans, it was estimated that there will be | This is a comment from the drug plans to inform CDEC deliberations. |

| Implementation issues | Response |
|---|---|
| [redacted] and [redacted] patients treated with cabotegravir LA in years 1 to 3, respectively.<br>In the scenario where cabotegravir LA is funded, the total drug cost of cabotegravir LA is anticipated to be $16,954,205 in year 1, $35,006,553 in year 2, and $40,205,665 in year 3. The resulting incremental budget impact from a drug program perspective was calculated to be $14,269,064 in year 1, $28,293,702 in year 2, and $30,136,388 in year 3. | |

FTC = emtricitabine; HPTN = HIV Prevention Trials Network; LA = long acting; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; TGW = transgender women.

# Clinical Evidence

## Systematic Review

### Description of Studies

Two pivotal trials (HPTN 083 and HPTN 084) provided evidence on the safety and efficacy of cabotegravir LA compared to daily oral TDF-FTC for PrEP in key at risk populations.

The HPTN 083 trial is an ongoing phase IIb/III, multicentre, double-blind, randomized, noninferiority trial designed to evaluate the efficacy and safety of injectable cabotegravir LA compared with oral TDF-FTC for PrEP in adult (18 years or older) gbMSM without HIV (evidenced by an HIV-test result that was nonreactive or negative). In total, 4,570 participants enrolled at 43 study centres (no study sites were in Canada) were randomized in a 1:1 ratio to receive either daily oral cabotegravir (30 mg tablets) and oral placebo TDF-FTC for up to 5 weeks (step 1), followed by cabotegravir LA injection (600 mg, intramuscular injection at weeks 5, 9, and every 8 weeks thereafter) plus daily oral placebo at step 2 (N = 2,283); or daily oral TDF-FTC (300 mg–200 mg fixed-dose combination tablet) and oral placebo cabotegravir for up to 5 weeks (step 1), followed by daily oral TDF-FTC plus placebo intramuscular injection at weeks 5, 9, and every 8 weeks thereafter at step 2 (N = 2,287). Of the participants randomized in each group, 4,566 were treated (2,281 participants in the cabotegravir LA group and 2,285 in the TDF-FTC group). The mean age of participants enrolled was 28 years. Findings presented in this submission are from the first preplanned interim analysis at the May 14, 2020, data cut-off.

The HPTN 084 trial is an ongoing phase III, multicentre, double-blind, randomized, superiority trial designed to evaluate the efficacy and safety of injectable cabotegravir LA against oral TDF-FTC for PrEP in HIV-negative adult (aged 18 to 45 years) cisgender women. In total, 3,224 participants from 20 study centres were randomized in a 1:1 ratio to receive either daily oral cabotegravir (30 mg tablets) and oral placebo TDF-FTC for up to 5 weeks (step 1), followed by cabotegravir LA injection (600 mg, intramuscular injection at weeks 5, 9, and every 8 weeks thereafter) plus daily oral placebo at step 2 (N = 1,614); or daily oral TDF-FTC (300 mg–200 mg fixed-dose combination tablet) and oral placebo cabotegravir LA for up to 5 weeks (step 1), followed by daily oral TDF-FTC plus placebo intramuscular injection at weeks 5, 9, and every 8

weeks thereafter at step 2 (N = 1,610). All participants enrolled were cisgender females and more than 99% were Black and younger than 35 years of age. Findings presented in this submission are from the second preplanned interim analysis conducted at the November 5, 2020, data cut-off.

Both trial designs included an oral lead-in phase (step 1), an injection phase (step 2), and an open-label extension phase (step 3). Key primary and secondary outcomes investigated were similar for both trials, which included documented incident HIV infections in steps 1 and 2 and number of participants experiencing grade 2 or higher clinical and laboratory adverse events. Other important outcomes assessed across trials included documented incident HIV infections in step 2, resistance mutations to study products, adherence to study product during step 2, and the incidence of sexually transmissible infections. Patient-reported outcomes were assessed using acceptability scale questionnaire and survey of attitudes and willingness to use cabotegravir and TDF-FTC using the Study Medication Satisfaction Questionnaire (SMSQ) (HPTN 083 only). The blinded phase in both trials was amended to an open-label design following results from planned interim analyses. All participants included the data analyses for this submission were blinded to study treatments.

### Efficacy Results

#### *Incident HIV Infections in Steps 1 and 2*

Based on the primary analysis in HPTN 083 and HPTN 084 that evaluated incident HIV-1 infections at steps 1 and 2 of the trials, the risk of HIV-1 infection was lower in the cabotegravir LA group than in the TDF-FTC group. More specifically, in HPTN 083, 13 HIV-1 infections were reported in the cabotegravir LA group (incidence rate per 100 person-years = 0.40; 95% CI, 0.22 to 0.69) versus 39 infections in the TDF-FTC group (incidence rate per 100 person-years = 1.22; 95% CI, 0.87 to 1.67), after 6,404 person-years of accumulated follow-up by the May 14, 2020, interim cut-off. The between-group difference in incidence rates was in favour of cabotegravir LA relative to TDF-FTC (between-group difference per 100 person-years = −0.82; 95% CI, −1.26 to −0.38). Noninferiority of cabotegravir LA to TDF-FTC was demonstrated; the estimated HR was 0.34 (95% CI, 0.18 to 0.62; P value = 0.0005), suggesting a 66% reduction in the incidence of HIV-1 infections in the cabotegravir LA group relative to TDF-FTC group. A revised data analysis from additional testing confirmed 12 HIV-1 infections in the cabotegravir LA group and 40 in the TDF-FTC group (new bias-adjusted HR = 0.31; 95% CI, 0.16 to 0.58). Supportive analyses conducted in those who were receiving the blinded study product were consistent with the primary analysis (estimated HR = 0.164; 95% CI, 0.06 to 0.47; P value = 0.0008) suggesting an 83.6% reduction in the incidence of HIV-1 infections in the cabotegravir LA group relative to TDF-FTC group).

In the HPTN 084 study, superiority of cabotegravir LA was demonstrated by the November 5, 2020, interim cut-off. In total, 40 incident HIV-1 infections were identified: 4 infections occurred in the cabotegravir LA group (incidence rate per 100 person-years = 0.20; 95% CI, 0.06 to 0.52) and 36 occurred in the TDF-FTC group (incidence rate per 100 person-years = 1.85; 95% CI, 1.3 to 2.56) after 3,907 person-years of accumulated follow-up. The between-group difference also favoured cabotegravir LA relative to TDF-FTC (between-group difference per 100 person-years = −1.65; 95% CI, −2.28 to −1.01). The estimated HR was 0.12 (95% CI, 0.05 to 0.31; P value < 0.0001), suggesting an 88% reduction in the incidence of HIV-1

infections in the cabotegravir LA group relative to TDF-FTC group. A revised data analyses from additional testing confirmed 39 incident HIV-1 infections, 3 occurring in the cabotegravir LA group (bias-adjusted HR = 0.1; 95% CI, 0.04 to 0.27), indicating a 90% reduction in the incidence of HIV-1 infections in the cabotegravir LA group relative to TDF-FTC group. Findings from 2 supportive analyses were consistent with the primary analysis (suggesting a 95% and 89% reduction in the incidence of HIV-1 infections in the cabotegravir LA group relative to TDF-FTC group in the blinded study product analysis and per-protocol analysis, respectively).

### *Incident HIV-1 Infections in Step 2 Only*

Both the HPTN-083 and HPTN-084 trials met the secondary end point, incident HIV-1 infections in step 2 only. In HPTN 083, 8 HIV-1 infections were identified in the cabotegravir LA group and 37 in the TDF-FTC group in step 2 only by the May 14, 2020, interim cut-off. The incidence rate per 100 person-years in the cabotegravir LA group was 0.27 (95% CI, 0.12 to 0.54) and 1.29 (95% CI, 0.91 to 1.77) in the TDF-FTC group (HR = 0.210; 95% CI, 0.10 to 0.45), suggesting a 79% reduction in the incidence of HIV-1 infections in the cabotegravir LA group relative to TDF-FTC group. The between-group difference in incidence rates favoured cabotegravir LA over TDF-FTC (between-group difference per 100 person-years = −1.01; 95% CI, −1.47 to −0.56).

In HPTN 084, 2 HIV-1 infections were identified in the cabotegravir LA group and 34 in the TDF-FTC group in step 2 only by the November 5, 2020, interim cut-off. The incidence rate per 100 person-years in the cabotegravir LA group was 0.11 (95% CI, 0.01 to 0.41) compared to 1.94 (95% CI, 1.35 to 2.72) in the TDF-FTC group (HR = 0.06; 95% CI, 0.01 to 0.24), suggesting a 94% reduction in the incidence of HIV-1 infections in the cabotegravir LA group relative to TDF-FTC group. The between-group difference in incidence rates also favoured cabotegravir LA over TDF-FTC (between-group difference per 100 person-years = −1.83; 95% CI, −2.5 to −1.16).

### *Viral Genotyping for Drug Resistance*

Viral genotyping of participants with HIV seropositivity was assessed as a secondary end point in study HPTN 083 and a tertiary end point in study HPTN 084. No new resistance mutations were reported among people with HIV seropositivity for both drug combinations in the trials. In the cabotegravir LA group in the HPTN 083 study, HIV genotyping results were obtained for 12 of the 15 patients in the cabotegravir LA group (1 failed testing and 2 did not have a viremic sample). Integrase resistance mutations were identified in 3 participants; nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance was identified in 3 other participants at the first viremic visit, including 1 nucleotide analogue reverse transcriptase inhibitor (NRTI) resistance.

In the TDF-FTC group of the HPTN 083 study, HIV genotyping results were presented for 40 of the 42 participants with HIV-1 (2 participants did not have a viremic visit). There were no resistance patterns identified in participants who had HIV-1 at baseline. Twelve participants showed resistance at the first viremic visit (7 had NNRTI resistance only, 1 had NRTI resistance only, 1 had single protease inhibitor resistance mutation only, and 3 had NNRTI and NRTI resistance). Ten participants who were identified with NNRTI resistance had 1 or more of the following mutations: K103N/S, Y181C, G190A/S, H221Y, P225H. In

4 participants with NRTI resistance (including 3 who had multiclass resistance), 3 had M184V/I and K65R mutations.

In the cabotegravir LA group of the HPTN 084 study, HIV genotyping results were available for 3 of 4 participants with HIV-1 (1 case did not have a viremic sample). One of 3 had an integrase mutation at the first viremic visit (L74I), which is considered a polymorphism, and it was also detected in participants in the TDF-FTC group.

In the TDF-FTC group of the HPTN 084 study, HIV genotyping results were obtained for 33 of 36 incident infections (2 failed testing; 1 did not have a viremic sample). A major NRTI mutation (M184V) was identified in 1 participant in addition to an NNRT resistance with the K103N mutation. Eight other participants had NNRTI resistance only (6 had K103N alone or with E138A or P225H; 1 had K101E alone; 1 had E138A alone). Integrase strand transfer inhibitor mutations or polymorphisms were detected in 10 samples (L74I, L74M, T97A, V151I, E157Q, G193E). For 1 participant with a dual-class resistance (NRTI and NNRTI), resistance observed in the first viremic visit was the same as the first site positive visit (at step 2, week 17; 33 days after the first HIV positive visit).

### *Adherence (Measured Through Pharmacokinetics)*

Adherence was assessed as a tertiary end point assessed within a subset of participants using each study medication in both trials. In the HPTN 083 study, adherence for cabotegravir LA injections was assessed in a random subset of 170 participants. Injection coverage was 91.5% of all person-year contributions for the subsample. Adherence to TDF-FTC was assessed in a random subset of 390 participants using plasma tenofovir concentrations and intraerythrocytic tenofovir-diphosphate concentrations collected as dried blood spots in the HPTN 083 study. In total, 74.2% of participants had tenofovir concentrations consistent with daily dosing (i.e., ≥ 40 ng/mL) and more than 86% had detectable tenofovir (≥ 0.31 ng/mL). Findings based on dried blood spots showed that 73% of samples yielded tenofovir-diphosphate concentrations consistent with 4 doses or more per week.

In a random subset of 150 participants in the HPTN 084 study, injection coverage in the cabotegravir LA group was 93% of all person-years contributions for the subsample of participants. TDF-FTC assessments were conducted in a random subset of 409 participants, of whom 41.9% had tenofovir concentrations consistent with daily dosing (≥ 40 ng/mL, corresponding to expected daily use concentration of TDF-FTC) and 55.9% had detectable tenofovir (≥ 0.31 ng/mL).

### Harms

The proportion of participants reporting at least 1 AE in the safety population set (on the blinded study product data set steps 1 and 2) were generally similar in both groups across trials (HPTN 083: 95% versus 94% in the cabotegravir LA and TDF-FTC groups, respectively; HPTN 084: 96% each in in the cabotegravir LA and TDF-FTC groups). Commonly reported AEs included injection site pain, decreased creatinine renal clearance, increased blood creatine phosphokinase, increased blood creatinine, and nasopharyngitis. Serious adverse events (SAEs) reported were 5% in each group in the HPTN 083 trial, and 2% each in both groups in the HPTN 084 trial.

There were 10 deaths reported in study HPTN 083, in the combined steps 1 and 2 (4 in the cabotegravir LA group; 6 in the TDF-FTC group), and 1 additional death reported in step 3. In study HPTN 084, 3 participants in the cabotegravir LA group died due to AEs. No deaths were reported in the TDF-FTC group. Withdrawals due to AEs were generally low in both groups in the 2 studies (HPTN 083: 6% and 4% in the cabotegravir LA and TDF-FTC groups, respectively; HPTN 084: 1% in each group).

Notable harms commonly reported in both trials included ISRs, hepatotoxicity, hypersensitivity reactions, rash, and neuropsychiatric events. ISRs were higher in the cabotegravir LA group in both trials (HPTN 083: 76% and 32% in the cabotegravir LA and TDF-FTC groups, respectively; HPTN 084, step 2: 38% and 11% in the cabotegravir LA and TDF-FTC groups, respectively).

### Critical Appraisal

HPTN 083 and HPTN 084 were multicentre trials with centres in Asia, South America, sub-Saharan Africa, and the US. There were no sites in Canada. The methods for randomization, allocation concealment, and double blinding maintenance were appropriate. Randomization was stratified by study site, and permuted blocks were used to ensure balance in treatment assignments within study sites. The use of placebo and the blinding of patients and outcome assessors mitigated concerns related to the risk of bias due to deviations from the intended interventions. The inclusion and exclusion criteria and patient characteristics at baseline were considered generalizable to Canada. Overall, the primary and key secondary outcomes assessed in both trials were considered appropriate and relevant to decision-making; they also adequately reflected measures of both efficacy and harms assessed in clinical practice. There were no notable imbalances in baseline demographics between treatment groups indicating that randomization was effective.

The use of the Poisson model to estimate the rate of HIV diagnosis in both trials was deemed appropriate by the review team but subject to 2 critical assumptions about the rate. The first assumption is that the rate of infection within the population is constant rate; the second is that the withdrawal and censoring were noninformative of an individual potentially acquiring HIV in the future. HPTN 083 was a noninferiority trial and the HR margin of 1.23 — referred to as M2 — was calculated based on an inverse-variance weighting of a meta-analysis of 3 RCTs of TDF-FTC against placebo in MSM (iPrex, IPERGAY, and PROUD). In the HPTN 084 study, the superiority of cabotegravir LA was demonstrated by an improvement in the incidence of HIV diagnoses. The analyses conducted were preplanned interim analyses, which can lead to an increased risk of overestimating the treatment effects (only 30% and 35% of the total number of HIV cases targeted for powering the final analyses of the HPTN 083 and HPTN 084 studies, respectively, were achieved at both interim data cut-offs). Missing data for the primary outcome across trials was addressed using noninformative censoring, supported by prespecified sensitivity analyses. Adjustments for type I error were accounted for key primary and secondary outcomes assessed in both trials. Neither study was powered for subgroup evaluations and no adjustments were made for multiple testing subgroup analyses. Treatment adherence was assessed using pharmacokinetic blood concentrations of study drugs in a random subset of participants for each treatment. There were differences between the 2 treatment groups in both trials which may have affected the efficacy of the primary outcome. There were notable differences in treatment adherence between the 2 groups within each trial and between the 2 trials. However, PK assessments of

plasma for drug concentrations may not be a comprehensive evaluation of adherence in participants due to known variabilities in drug metabolism across individuals. Both trials provided direct evidence of the comparative efficacy of cabotegravir LA against an available PrEP option in Canadian practice; however, there is a lack of evidence on the long-term therapeutic benefit and safety of cabotegravir LA beyond the duration of both trials, which is a source of uncertainty. The dosing regimen of TDF-FTC in both trials aligned with Canadian practice. The duration of follow-up was considered appropriate and adequate to identify HIV-1 events (i.e., incident HIV-1 infection) and a difference between the 2 groups. Although follow-up frequencies and adherence measurements assessed during the trials were considered appropriate, they may not be reflective of current Canadian guideline recommendations. There were no concerns with the concomitant medications administered that may have impacted on cabotegravir LA's efficacy.

### GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect based on a threshold informed by the clinical expert consulted for this review for documented incident HIV infections. There is no established minimal important difference, and the clinical expert consulted for this review could not provide a threshold of important difference so the target of the certainty of evidence assessment was the presence or absence of any (non-null) effect. Other targets for the certainty of evidence assessment were the presence or absence of any effect for the proportion of patients reporting SAEs and ISRs.

#### *Results of GRADE Assessments*

The GRADE assessments included an evaluation of the main outcomes considered important by clinicians, patient groups, and stakeholders. The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: documented incident HIV diagnoses, harms (SAE and ISR). Two outcomes included in the report (resistance mutations to study products among participants with HIV-1 seropositivity, and adherence to study product) were not included on the GRADE table.

Table 3 and Table 4 presents the GRADE summary of findings for cabotegravir LA versus TDF-FTC for cisgender men and TGW gbMSM, and cisgender women, respectively, at increased risk of acquiring HIV-1 infections.

## Long-Term Extension Studies

No long-term extension studies were submitted for this review.

## Indirect Comparisons

### Description of Studies

One sponsor-conducted indirect treatment comparison compared cabotegravir LA to placebo or no PrEP regarding the effectiveness for reducing HIV transmissions using a Bayesian NMA.

### Efficacy Results

In the Bayesian fixed-effect NMA, based on 10 trials, cabotegravir LA demonstrated improved effectiveness in reducing HIV transmission compared to placebo or no PrEP (HPTN 083 population [gbMSM and TGW]: drug effectiveness = 91.10%; 95% credible interval [CrI], 82.87% to 95.95%; HPTN 084 population [cisgender women]: 92.52%; 95% CrI, 83.02% to 97.38%).

## Table 3: Summary of Findings for Cabotegravir LA Versus TDF-FTC for Cisgender Men and TGW gbMSM at Risk of Acquiring HIV-1 (HPTN 083)

| Outcome and follow-up | Patients (studies), N | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Cabotegravir LA | TDF-FTC | Difference | | |
| **Documented HIV-1** | | | | | | |
| Incidence rate of HIV-1 infections in steps 1 and 2 (n/100 PY)<br>Follow-up: 6,404 total person-years | 4,561 (1 RCT) | 0.40 per 100 PY (0.22 to 0.69) | 1.22 per 100 PY (0.87 to 1.67) | 0.82 fewer HIV-1 incident HIV-1 infections per 100 PY (0.38 to 1.26 fewer) | High[a] | Cabotegravir LA results in a reduction in the incidence of HIV-1 when compared to TDF-FTC in gbMSM and TGW. The clinical importance of the reduction is unclear. |
| **Harms** | | | | | | |
| Proportion of participants with SAEs<br>Follow-up: approximately 160 weeks cumulative follow-up (before data cut-off) | 4,566 (1 RCT) | 5 per 100 (NR) | 5 per 100 (NR) | 0.36 more SAEs per 100 (0.9 fewer to 1.6 more) | Moderate[b] | Cabotegravir LA likely results in fewer to more SAEs when compared to TDF-FTC in gbMSM and TGW. The clinical |

| Outcome and follow-up | Patients (studies), N | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Cabotegravir LA | TDF-FTC | Difference | | |
| | | | | | | importance of the reduction is unclear. |
| Proportion of participants with injection site reactions (n/100)<br>Follow-up: (approximately. 160 weeks cumulative follow-up [before data cut-off]) | 4,198 (1 RCT) | 82 per 100 (NR) | 35 per 100 (NR) | 47.4 more ISR per 100 (44.8 to 50 more ISRs) | High[c] | Cabotegravir LA likely results in more injection site reactions when compared to TDF-FTC in gbMSM and TGW. |

CI = confidence interval; FTC = emtricitabine; gbMSM = gay bisexual men who have sex with men; NR = not reported; PY = person-years; RCT = randomized controlled trial; SAE = serious adverse events; TDF = tenofovir disoproxil fumarate; TGW = transgender women.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

HPTN 083 is a noninferiority phase IIb/II study that enrolled cisgender men without HIV-1 and transgender women who have sex with men, who were at risk of acquiring HIV-1 infections.

[a]There is no established minimal important difference (MID), and the clinical expert consulted for this review could not provide a threshold of important difference; therefore, the null was used. Not rated down for imprecision because the CI of the difference between the 2 groups did not overlap with the null (0). The review team judged that the point estimate and the 95% CI for the between-group difference suggested a benefit. Although results were from an interim analysis, certainty of evidence was not rated down by the review team because appropriate methods (i.e., Lan DeMets modification of the O'Brien-Fleming stopping bounds method) were used to account for alpha spending before interim analysis.

[b]There is no established MID and the clinical expert consulted for this review could not provide a threshold of important difference; therefore, the null was used. Rated down 1 level for serious imprecision. The lower bound of the 95% CI for the between-group difference was less than zero while the upper bound was greater than zero suggested no clinically important difference between the 2 groups.

[c]There is no established MID and the clinical expert consulted for this review did not provide a threshold of important difference. The review team judged that the MID of harm for ISR was null given that both treatments consist of 2 formulations: an oral and intramuscular injections. Not rated down for imprecision as CI of the difference between the 2 groups did not overlap with the null (0) and fell beyond the clinically meaningful benefit threshold, indicating harm.

Source: HPTN 083 Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

## Table 4: Summary of Findings for Cabotegravir LA Versus TDF-FTC for Cisgender Women at Risk of Acquiring HIV-1 (HPTN 084)

| Outcome and follow-up | Patients (studies), N | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Cabotegravir LA | TDF-FTC | Difference | | |
| **Documented HIV-1** | | | | | | |
| Incidence rate of HIV-1 infections in steps 1 and 2 (n/100 PY)<br>Follow-up: 3,907 total person-years | 3,224 (1 RCT) | 0.20 per 100 PY (0.06 to 0.52) | 1.85 per 100 PY (1.30 to 2.56) | 1.65 fewer HIV-1 incident HIV-1 infections per 100 PY (1.01 to 2.28 fewer) | High[a] | Cabotegravir LA results in a reduction in the incidence of HIV-1 when compared to TDF-FTC in cisgender women. The clinical importance of |

| Outcome and follow-up | Patients (studies), N | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | Cabotegravir LA | TDF-FTC | Difference | | |
| | | | | | | the reduction is unclear. |
| **Harms** | | | | | | |
| Proportion of participants with SAEs (n/100)<br>Follow-up: approximately 158 weeks cumulative follow-up up [before data cut-off] | 3,224 (1 RCT) | 2 per 100 (NR) | 2 per 100 (NR) | 0.005 fewer SAE reactions per 100 (0.98 fewer to 0.97 more) | Moderate[b] | Cabotegravir LA likely results in fewer to more SAEs when compared to TDF-FTC in cisgender women. The clinical importance of the reduction is unclear. |
| Proportion of participants with injection site reactions (n/100)<br>Follow-up: approximately 158 weeks cumulative follow-up (before data cut-off) | 3, 035 (1 RCT) | 38 per 100 | 11 per 100 | 27.1 more ISR per 100 (24.2 to 30 more ISR) | High[c] | Cabotegravir LA likely results in more injection site reactions when compared to TDF-FTC in cisgender women. |

CI = confidence interval; FTC = emtricitabine; NR = not reported; PY = person-years; RCT = randomized controlled trial; SAE = safety adverse events; TDF = tenofovir disoproxil fumarate; TGW = transgender women.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

HPTN 084 is a phase III superiority trial which enrolled cisgender women without HIV who were at risk of acquiring HIV-1 infections.

[a]There is no established MID and the clinical expert consulted for this review could not provide a threshold of important difference; therefore, the null was used. Not rated down for imprecision as CI of the difference between the 2 groups did not overlap with the null (0). The review team judged that the point estimate and the 95% CI for the between-group difference suggested a benefit. Although results were from an interim analysis, certainty of evidence was not rated down by the review team because appropriate methods (i.e., Lan DeMets modification of the O'Brien-Fleming stopping bounds method) were used to account for alpha spending before interim analysis.

[b]There is no established MID and the clinical expert consulted for this review could not provide a threshold of important difference; therefore, the null was used. Rated down 1 level for serious imprecision. The lower bound of the 95% CI for the between-group difference was less than zero while the upper bound was greater than zero suggested no clinically important difference between the 2 groups.

[c]There is no established MID and the clinical expert consulted for this review did not provide a threshold of important difference. The review team judged that the MID of harm for injection site reaction was null given that both treatments consist of 2 formulations: an oral and intramuscular injections. Not rated down for imprecision as CI of the difference between the 2 groups did not overlap with the null (0) and fell beyond the clinically meaningful benefit threshold, indicating harm.

Source: HPTN 084 Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

### Harms Results

No harms results were reported in the sponsor-submitted NMA.

### Critical Appraisal

The validity of the NMA results is dependent on key assumptions (e.g., homogeneity and consistency). Network homogeneity and consistency could not be determined based on insufficient reporting of study characteristics and a sparse linear network without a closed loop. Based on the available information,

there was evidence of heterogeneity between the included studies based on study designs (e.g., blinding), patient populations (e.g., mixing patients who inject drugs and patients who do not inject drugs), and trial characteristics that were unaccounted for in the analysis. These limitations result in uncertainty in the magnitude of the relative treatment effect estimates between cabotegravir LA versus placebo or no PrEP.

### Studies Addressing Gaps in the Evidence From the Systematic Review

Two studies conducted in adolescent populations were submitted for this review. HPTN 083-01 and HPTN 084-01 were both open-label, single-arm, phase IIb, substudies of the main pivotal trials (HPTN 083 and HPTN 084) assessing the safety, tolerability, and acceptability of cabotegravir LA in adolescent participants without HIV-1 (younger than 18 years), cisgender females, and males (identifying as MSM or TGW) at risk of acquiring HIV-1.

#### Efficacy Results

No efficacy outcomes were assessed in both trials.

#### Harms

No new safety concerns were identified. ISRs reported in both studies were of grade 1 or 2 and did not result in study drug discontinuations. Cabotegravir LA injections were also well tolerated with no participant discontinuing treatment prematurely due to intolerability of injection or burden of study procedures.

#### Critical Appraisal

There is uncertainty about whether the sample size and power calculations for both studies was sufficient to assess the efficacy of cabotegravir LA in the 2 studies (total sample size of participants enrolled for HPTN 083-01 was N = 9 and N = 55 for HPTN 084). The lack of a comparative and the absence of any assessments related to primary efficacy outcomes limited the interpretability of the magnitude of the benefit of cabotegravir LA reducing new HIV-1 infections in adolescent populations. Thus, no definitive conclusions could be drawn; however, no safety signals were identified.

## Economic Evidence

### Cost and Cost-Effectiveness

### Table 5: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Markov Model |
| **Target population** | Adults at increased risk of acquiring HIV-1 (men who have sex with men, transgender women who have sex with men, and cisgender women) and who are eligible to receive PrEP. |
| **Treatment** | Cabotegravir |

| Component | Description |
|---|---|
| **Dose regimen** | • With oral lead-in: One 30 mg tablet per day for at least 28 days. Within 3 days of completing the oral lead-in, 3 mL (600 mg) injection and then a second 3 mL (600 mg) injection 1 month (28 days) later, followed by 3 mL (600 mg) injection month 4 and every 2 months thereafter.<br>• Without oral lead-in: 3 mL (600 mg) injection months 1 and 2, followed by 3 mL (600 mg) injection month 4 and every 2 months thereafter. |
| **Submitted price** | Cabotegravir, 30 mg tablet: $30.08 per tablet<br>Cabotegravir, 600 mg/3 mL extended-release injectable solution: $1,710 per vial |
| **Submitted treatment cost** | Year 1: $11,252 (with oral lead-in), ≥ year 2: $10,260; $10,260 per year without oral lead-in |
| **Comparators** | No PrEP: the absence of prophylactic treatment to prevent HIV infection<br>TDF-FTC<br>FTC-TAF (scenario analysis only) |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, life-years |
| **Time horizon** | Lifetime (100 years) |
| **Key data sources** | Clinical trials: HPTN-083, HPTN-084<br>Sponsor-submitted ITC |
| **Key limitations** | • The clinical review of the submitted ITC found considerable imprecision in the estimate of HIV prevention. Although cabotegravir was associated with improvements relative to no PrEP, a definitive conclusion could not be drawn due to heterogeneity in the study design and patient characteristics.<br>• The baseline incidence of HIV in the patient population may not reflect the most up-to-date evidence base. Values were obtained from placebo arms from 2 of 10 trials included in a systematic review.<br>• Sponsor's base case included spillover costs and QALYs experienced by an untreated population. This approach is not aligned with submission requirements for reimbursement reviews and contributed incremental benefit with highly questionable validity.<br>• The sponsor's approach to characterizing parameter uncertainty did not follow recommended practice for several important inputs. The baseline HIV incidence rate, relative treatment effects, and other inputs were programmed without incorporating uncertainty in the estimated value. Consequently, decision uncertainty was not accurately reflected in the model results. |
| **Reanalysis results** | • The review team's base case addressed some of the identified limitations by including treatment administration costs, removing of spillover effects, changing the source of baseline HIV incidence rate to the values estimated from the submitted ITC, and assuming 100% oral PrEP adherence.<br>• Cabotegravir and TDF-FTC were the only comparators on the efficiency frontier. Cabotegravir was more costly and more effective compared to TDF-FTC, resulting in an ICER of $29,283 (incremental costs: $2,778; incremental QALYs: 0.09) |

FTC = emtricitabine; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; PrEP = pre-exposure prophylaxis; QALY = quality-adjusted life-year; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

## Budget Impact

The review team identified 2 limitations in the sponsor's base case. These related to the underestimation of the market size and the absence of an open population. A scenario analysis was performed to explore how an increase to the proportion of adults eligible for PrEP would affect the estimated budget impact.

In the submitted base case, the budget impact from the introduction of cabotegravir was estimated to be $14,269,064 in year 1, $28,293,702 in year 2, and $30,136,388 in year 3. The 3-year net budget impact of cabotegravir was estimated to be $72,699,154. Findings from the review team's scenario analysis illustrated how an increase to the proportion of adults eligible for PrEP would increase the estimated budget impact.

## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

**Meeting date**: June 27, 2024

**Regrets**: Two expert committee members did not attend.

**Conflicts of interest**: None

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