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Cost-Effectiveness Analysis of CAB-LA for PrEP in the United States

At the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2022 conference on May 10, 2022, in Washington, DC, Ashley E. Davis, PhD, director of health economics at RTI Health Solutions, presented the findings from a cost-effectiveness analysis of cabotegravir long-acting for PrEP in the United States, where it was 1 of 3 winners from more than 1400 submissions for "Best General Podium Research Presentation".¹ RTI Health Solutions received funding for this study from ViiV Healthcare. ViiV Healthcare sponsored the development of the model. This article summarizes the presentation highlights and was not peer reviewed.

Davis AE, Brogan AJ, Mellott CE, Fraysse J, Oglesby A. Cost-effectiveness analysis of CAB-LA for PrEP in the United States. Presented at the ISPOR 2022 Conference; May 10, 2022; Washington, DC.²

INTENDED FOR DISTRIBUTION ONLY TO PAYERS, FORMULARY COMMITTEES, OR SIMILAR ENTITIES FOR HEALTHCARE ECONOMIC ANALYSIS PURSUANT TO SECTION 114 OF THE FOOD AND DRUG MODERNIZATION ACT TO FACILITATE DRUG SELECTION, ON A POPULATION BASIS, FOR COVERAGE OR REIMBURSEMENT.

INDICATION

APRETUDE (cabotegravir 200 mg/mL) extended-release injectable suspension is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating APRETUDE (with or without an oral lead-in with oral cabotegravir) for HIV-1 PrEP.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: RISK OF DRUG RESISTANCE WITH USE OF APRETUDE FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Individuals must be tested for HIV-1 infection prior to initiating APRETUDE or oral cabotegravir, and with each subsequent injection of APRETUDE, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Drug-resistant HIV-1 variants have been identified with use of APRETUDE by individuals with undiagnosed HIV-1 infection. Do not initiate APRETUDE for HIV-1 PrEP unless negative infection status is confirmed. Individuals who become infected with HIV-1 while receiving APRETUDE for PrEP must transition to a complete HIV-1 treatment regimen.

CONTRAINDICATIONS

- Do not use APRETUDE in individuals:
 - with unknown or positive HIV-1 status
 - with previous hypersensitivity reaction to cabotegravir
 - receiving carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, and rifapentine

STATEMENT OF MATERIAL DIFFERENCES WITH THE FDA-APPROVED LABELING

The information presented in this piece contains material differences from the label, as the population included in the model is more narrow and only accounts for data collected from high-risk men who have sex with men (MSM), transgender women (TGW), and cisgender women (CGW) aged 18 years or older. Cabotegravir long-acting (CAB-LA) was only studied compared with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in pivotal trials. Generic FTC/TDF and emtricitabine/tenofovir alafenamide (FTC/TAF) are included for modeling purposes only, as the rate of efficacy of CAB-LA vs these drugs has not been established. The model makes certain assumptions when there are data gaps, including assumptions relating to persistence, adherence, and secondary infections.

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BACKGROUND

Preexposure prophylaxis (PrEP) is effective in preventing HIV in individuals who are at an increased risk of acquiring HIV infection.³ Oral PrEP was first approved for adults in the United States in 2012.⁴ There are 2 oral options currently available in the United States: emtricitabine/tenofovir alafenamide (FTC/TAF) and emtricitabine/tenofovir disoproxil fumarate (FTC/TDF).⁴ FTC/TDF is the only oral PrEP option approved for use by CGW.⁴

Oral PrEP is highly underutilized by at-risk individuals who could benefit from PrEP. The Centers for Disease Control and Prevention (CDC) estimates that just 24.7% of PrEP-eligible individuals were using it in 2020.⁵ Cabotegravir long-acting (CAB-LA), branded in the US as APRETUDE (cabotegravir extended-release injectable suspension), was approved in the United States in 2021 as an injectable PrEP option for individuals at risk of acquiring HIV-1 infection through sex. APRETUDE is administered as an intramuscular injection by a healthcare professional every 2 months after 2 initiation injections administered 1 month apart. Adherence to the dosing schedule is strongly recommended.⁶

APRETUDE was studied in two large-scale, multinational, randomized (1:1), double-blind, placebo-controlled trials (HIV Prevention Trial Network [HPTN] 083 and HPTN 084), comparing the safety and efficacy of APRETUDE with daily oral TDF/FTC for HIV-1 prevention among populations at risk of acquiring HIV-1.⁶⁻¹⁰ HPTN 083 included HIV-1 uninfected men and TGW who have sex with men, and HPTN 084 included HIV-1 uninfected CGW.

COST EFFECTIVENESS ANALYSIS OF CAB-LA FOR PrEP IN THE UNITED STATES

At the ISPOR 2022 conference, held May 15-18, 2022, in Washington, DC, Ashley E. Davis, PhD, director of health economics at RTI Health Solutions, presented the findings from a cost-effectiveness analysis of cabotegravir long-acting for PrEP in the United States.² The objective of the study was to estimate the lifetime cost-effectiveness of

initiating CAB-LA compared with generic TDF/FTC.² ViiV Healthcare sponsored the development of the model.

MODEL OVERVIEW²

A Markov model was developed to compare the use of PrEP options assuming a 5-year duration of high-risk behavior (eg, PrEP eligibility) over a lifetime horizon to fully capture the costs and effects of HIV acquisition (**Figure**).² Since model completion and presentation, subsequent data analyses exist that are not incorporated. Notably, HIV incidence and PrEP breakthrough resistance in the model reflect the randomized blinded phase of HPTN 083 and HPTN 084 as represented in the full Prescribing Information.

MSM, TGW, and CGW at high risk of acquiring HIV-1 infection entered the model and were assigned to either CAB-LA or generic FTC/TDF. Over time, they could choose to continue receiving their initial PrEP option, transition to a second PrEP option, or discontinue PrEP. CGW initiating PrEP with FTC/TDF did not have a second PrEP option because FTC/TAF is not approved in this population.

The model assumes eligible individuals on PrEP were at a reduced risk of acquiring HIV infection and incurred PrEP-related costs. Those on CAB-LA may experience injection-site reactions (ISRs) based on the frequency of ISRs reported in HPTN 083 and 084 clinical trials.¹¹ Those who acquire HIV in the model are assumed to incur lifetime HIV-related costs and quality-adjusted life year (QALY) losses, may transmit HIV to their partners, and may also develop PrEP-related breakthrough resistance.

INPUTS AND ASSUMPTIONS

Population and PrEP Use Characteristics

PrEP adherence, persistence, and switching were explicitly modeled. In the base-case analysis, individuals receiving oral PrEP were assumed to have the same adherence as those receiving FTC/TDF in the HPTN 083 clinical trial (subset analysis, tertiary endpoint), and

IMPORTANT SAFETY INFORMATION FOR APRETUDE (*CONTINUED*)

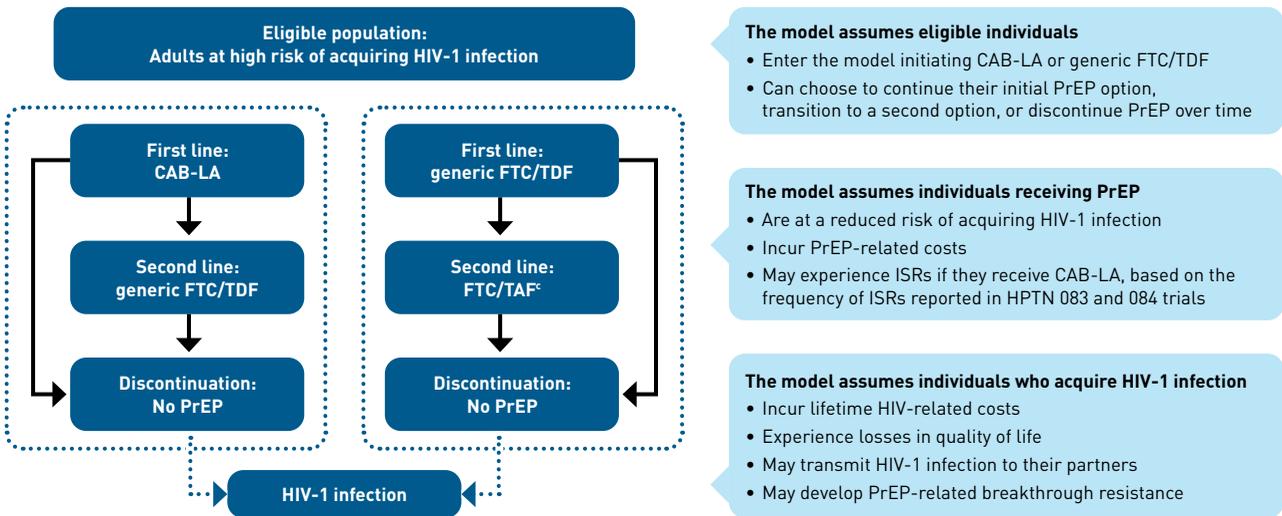
WARNINGS AND PRECAUTIONS

Comprehensive Management to Reduce the Risk of HIV-1 Infection:

- Use APRETUDE as part of a comprehensive prevention strategy, including adherence to the administration schedule and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs). APRETUDE is not always effective in preventing HIV-1 acquisition. Risk for HIV-1 acquisition includes, but is not limited to, condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network. Inform, counsel, and support individuals on the use of other prevention measures (e.g., consistent and correct condom use; knowledge of partner[s] HIV-1 status, including viral suppression status; regular testing for STIs)

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Figure. Study Design and Model Overview^{2,a,b}



CAB-LA, cabotegravir long-acting; CGW, cisgender women; FTC/TAF, emtricitabine/tenofovir alafenamide; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; ISRs, injection-site reactions; PrEP, preexposure prophylaxis.

^aMarkov model to compare PrEP options was developed with a 1-month cycle length, a 5-year duration of HIV risk, and a lifetime time horizon.

^bCAB-LA was only studied compared with FTC/TDF in pivotal trials. Generic FTC/TDF and FTC/TAF are included for modeling purposes only.

^cCGW were not eligible for this second-line option.

oral PrEP costs were adjusted appropriately. In a sensitivity analysis, adherence was varied and allowed to affect the cost and efficacy of oral PrEP for MSM and TGW and only the cost of oral PrEP for CGW because PrEP adherence has not been widely studied for this subgroup. The model defined PrEP adherence as the extent to which an individual acts in accordance with the prescribed interval and dose of a dosing regimen. As a conservative approach, individuals receiving CAB-LA were assumed to have 100% adherence and, therefore, to incur 100%

of acquisition costs throughout use. These assumptions did not alter effectiveness, which was taken from HPTN 083 for MSM and TGW and from HPTN 084 for CGW.

PrEP persistence informed the percentage of modeled individuals remaining on PrEP over time from month 0 to month 12. The percentages of people remaining on CAB-LA and oral PrEP were 100% at month 0, 84.2% and 70.2% at month 6, and 68.9% and 57.4% at month 12, respectively.^{2,12} For the purposes of the model, individuals on CAB-LA

IMPORTANT SAFETY INFORMATION FOR APRETUDE (cabotegravir) (CONTINUED)

WARNINGS AND PRECAUTIONS

Comprehensive Management to Reduce the Risk of HIV-1 Infection: (continued)

- Use APRETUDE only in individuals confirmed to be HIV-1 negative. HIV-1 resistance substitutions may emerge in individuals with undiagnosed HIV-1 infection who are taking only APRETUDE, because APRETUDE alone does not constitute a complete regimen for HIV-1 treatment. Prior to initiating APRETUDE, ask seronegative individuals about recent (in past month) potential exposure events and evaluate for current or recent signs or symptoms consistent with acute HIV-1 infection (e.g., fever, fatigue, myalgia, skin rash). If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, use a test approved or cleared by the FDA as an aid in the diagnosis of acute HIV-1 infection
- When using APRETUDE, HIV-1 testing should be repeated prior to each injection and upon diagnosis of any other STIs
- Additional HIV testing to determine HIV status is needed if an HIV-1 test indicates possible HIV-1 infection or if symptoms consistent with acute HIV-1 infection develop following an exposure event. If HIV-1 infection is confirmed, then transition the individual to a complete HIV-1 treatment
- Counsel HIV-1 uninfected individuals to strictly adhere to the recommended dosing and testing schedule for APRETUDE

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were assumed to be 20% more persistent than those on oral PrEP. The modelers assumed that a long-acting injectable option may address certain known barriers to oral PrEP. This assumption was used due to the lack of real-world or long-term persistence data on CAB-LA. In the model, individuals were also able to transition from their first PrEP option to a second PrEP option or to no PrEP according to published literature and conservative assumptions.

Clinical Data and Health Effects²

While receiving PrEP, individuals were at a reduced risk of acquiring HIV infection. Among MSM and TGW, HIV incidence without PrEP was 3.25 events per 100 person-years based on published literature.^{12,13} HIV incidence without PrEP for at-risk CGW was estimated to be 2.73 events per 100 person-years using a weighted-average approach informed by published literature and publicly available data.¹²⁻¹⁴ HIV incidence rates for MSM and TGW receiving CAB-LA or oral PrEP (FTC/TDF) were taken directly from HPTN 083. HIV incidence rates for CGW receiving CAB-LA or oral PrEP (FTC/TDF) were taken directly from HPTN 084.⁶

PrEP and HIV-Related Costs²

Over time, modeled individuals incurred PrEP-related costs and possibly lifetime HIV-related care costs.

PrEP Costs

PrEP costs included medication acquisition, administration, and monitoring costs. PrEP acquisition costs were based on indicated dosing and RED BOOK wholesale acquisition costs. The costs for CAB-LA were based on individuals receiving 7 injections in Year 1 and 6 injections in subsequent years, according to the CAB-LA dosing schedule.¹⁵ The cost of FTC/TDF was based on the lowest cost among the available generic options.¹⁵ Additional PrEP costs included costs for injection administration, routine physician visits, and monitoring tests recommended by CDC guidance for individuals receiving each PrEP option (Table 1).^{2,15,16}

Individuals receiving CAB-LA could experience injection-site reactions, and incidence rates by severity were based on the HPTN 083 and HPTN 084 studies. Injection-site reactions can occur at any time, but the model excludes these costs after Year 1 because reports of ISRs from HPTN 083 and 084 decreased over time.

HIV-related Costs

Individuals who acquired HIV-1 infection in the model incurred the lifetime costs of HIV-related care, including the cost of antiretroviral treatment and ongoing monitoring. The total discounted lifetime cost of HIV-related care used in the model was \$939,946. People experiencing seroconversion without resistance were assumed to receive a low-cost, single-tablet regimen. Individuals who acquired HIV while receiving PrEP could develop PrEP-related breakthrough resistance. Incidence of integrase strand transfer inhibitor (INSTI) and nucleoside reverse transcriptase inhibitor (NRTI) resistance were taken from the HPTN 083 study. People experiencing seroconversion with INSTI or NRTI resistance were assumed to receive other appropriate antiretrovirals with incrementally higher associated costs shown in Table 2.^{2,15,17}

RESULTS

Base-Case Result²

Overall, CAB-LA was cost-effective compared with lowest-cost generic FTC/TDF with an incremental cost per QALY gained of \$46,843.¹⁸

One-Way and Probabilistic Sensitivity Analysis Results

A one-way sensitivity analysis was conducted to assess the sensitivity of the model results to changes in uncertain parameters. Results showed that the incremental cost-effectiveness ratio (ICER) was most sensitive to changes in HIV incidence for MSM and TGW while receiving FTC/TDF or CAB-LA and to changes in adherence to oral PrEP.¹⁸ Overall, the ICER generally remained below \$100,000 when parameters were varied across their 95% CIs, suggesting the stability of the predicted results.²

IMPORTANT SAFETY INFORMATION FOR APRETUDE (cabotegravir) (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Potential Risk of Resistance with APRETUDE:

- There is a potential risk of developing resistance to APRETUDE if an individual acquires HIV-1 either before, while taking, or following discontinuation of APRETUDE. To minimize this risk, it is essential to clinically reassess individuals for risk of HIV-1 acquisition and to test before each injection to confirm HIV-1–negative status. Individuals who are confirmed to have HIV-1 infection must transition to a complete HIV-1 treatment. If individuals at continuing risk of HIV-1 acquisition discontinue APRETUDE, alternative forms of PrEP should be considered and initiated within 2 months of the final injection of APRETUDE

Long-Acting Properties and Potential Associated Risks with APRETUDE:

- Residual concentrations of cabotegravir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer). Take the prolonged-release characteristics of cabotegravir into consideration and carefully select individuals who agree to the required every-2-month injection dosing schedule because non-adherence or missed doses could lead to HIV-1 acquisition and development of resistance

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A probabilistic sensitivity analysis also was conducted. CAB-LA was found to be cost-effective compared with FTC/TDF in 85% of simulations at a willingness-to-pay threshold of \$100,000 per QALY gained.²

Scenario Analysis Results²

Analyses were conducted to examine the results for PrEP use scenarios, population subgroups disproportionately impacted by the epidemic, and varying assumptions about the duration of HIV risk, while holding all other variables constant.

The first scenario tested CAB-LA vs no PrEP. As PrEP is highly underutilized in the United States, no PrEP is a relevant comparator for many eligible individuals.¹³ The second scenario tested oral PrEP adherence observed in a real-world setting rather than in a clinical trial setting. In both cases, CAB-LA increased QALYs while lowering costs for the health system.² When assuming a willingness-to-pay threshold of \$100,000 per QALY gained, CAB-LA was cost-effective or cost saving compared with FTC/TDF for most population subgroups, including MSM and TGW, MSM of color, and CGW (Table 3).^{2,7,12-14,19-21} CAB-LA slightly exceeded the willingness-to-pay threshold when limited to white MSM. CAB-LA was also found to be cost-effective when longer or shorter durations of HIV risk were tested. The incremental cost per QALY gained at 2 years was \$40,432 vs \$83,206 at 10 years.

LIMITATIONS²

Results remained consistent under varied circumstances, but the cost-effectiveness model has limitations that should be considered when interpreting the results. Limitations included:

- Lack of available data inputs are typical for pharmacoeconomic analyses. All inputs with uncertainty were tested in a sensitivity analysis, and ISPOR good research practices in modeling were followed.
- Some PrEP-eligible population characteristics are not well-documented, but the model used published data and conservative estimates when necessary.

Table 1. PrEP Costs in Year 1 and Year 2+^{2,15,16,a}

PrEP costs	Year 1 ^b	Year 2+ ^b
Monthly wholesale acquisition cost		
CAB-LA ^c	\$2158	\$1850
FTC/TDF	\$30	\$30
FTC/TAF	\$2039	\$2039
Annual administration and visit costs		
CAB-LA	\$746	\$640
Oral PrEP	\$368	\$368
Annual monitoring costs (MSM and TGW/CGW)		
CAB-LA	\$1060/\$903	\$950/\$794
FTC/TDF	\$763/\$575	\$803/\$615
FTC/TAF	\$776/NA ^d	\$817/NA ^d
Injection-site reaction management costs per episode ^e		
Mild	\$0.00	NA ^f
Moderate	\$4.51	NA
Severe	\$187.58	NA

CAB-LA, cabotegravir long-acting; CGW, cisgender women; FTC/TAF, emtricitabine/tenofovir atafenamide; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life years; TGW, transgender women.

^aCAB-LA was only studied compared with FTC/TDF in pivotal trials. FTC/TAF is included for modeling purposes only.

^bIndividuals on CAB-LA are assumed to have 7 injections in year 1 and 6 injections in years 2+.

^cCAB-LA 1-month cost was derived from the 2-month vial cost.

^dFTC/TAF is not indicated for use by cisgender women.

^eInjection-site reactions were associated with management costs that were estimated by severity, assuming mild reactions required no medical management, moderate reactions were managed with over-the-counter medication, and severe reactions additionally required a physician visit.

^fInjection-site reactions can occur at any time, but the model excludes these costs after Year 1 because reports of injection-site reactions from HPTN 083 and HPTN 084 decreased over time.

IMPORTANT SAFETY INFORMATION FOR APRETUDE (cabotegravir) (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Hypersensitivity Reactions:

- Serious or severe hypersensitivity reactions have been reported in association with other integrase inhibitors and could occur with APRETUDE
- Discontinue APRETUDE immediately if signs or symptoms of hypersensitivity reactions develop. Clinical status, including liver transaminases, should be monitored and appropriate therapy initiated

Hepatotoxicity:

- Hepatotoxicity has been reported in a limited number of individuals receiving cabotegravir with or without known pre-existing hepatic disease or identifiable risk factors
- Clinical and laboratory monitoring should be considered and APRETUDE should be discontinued if hepatotoxicity is suspected and individuals managed as clinically indicated

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Table 2. HIV-related Costs^{2,15,17}

HIV-related costs	Value
Discounted lifetime HIV-related care cost ^a	\$939,946
PrEP-related breakthrough resistance costs ^b	
INSTI incremental cost	\$17,199
NRTI incremental cost	\$17,875
Years of differentiation due to resistance	16.2

INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PrEP, pre-exposure prophylaxis.

^aApplied to primary and secondary HIV-1 infections.

^bPeople experiencing seroconversion without resistance were assumed to receive a low-cost, single-tablet regimen, whereas people experiencing seroconversion with INSTI or NRTI resistance were assumed to receive other appropriate antiretrovirals.

- HIV incidence for TGW and CGW not on PrEP was assumed or calculated, respectively, based on published data, due to lack of extensive studies and publications in these populations.
- Estimated HIV incidence while receiving PrEP was taken from clinical trials HPTN 083 and 084, which did not include TAF/FTC and may not mirror real-world use.
- No utility decrement was applied while receiving PrEP because it was assumed that individuals who choose to receive PrEP view their choice positively.
- Estimate for the years of PrEP-related breakthrough resistance differentiation was based on the most recent available published data.

CONCLUSIONS²

Overall, CAB-LA is predicted to be cost-effective compared with daily oral FTC/TDF for individuals at risk of acquiring HIV-1 infection.² •

For inquiries relating to this model, please contact Aimee Metzner, aimee.a.metzner@viiivhealthcare.com

IMPORTANT SAFETY INFORMATION FOR APRETUDE (cabotegravir) (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Depressive Disorders:

- Depressive disorders (including depression, depressed mood, major depression, persistent depressive disorder, suicidal ideation or attempt) have been reported with APRETUDE
- Promptly evaluate patients with depressive symptoms

Risk of Reduced Drug Concentration of APRETUDE Due to Drug Interactions:

- The concomitant use of APRETUDE and other drugs may result in reduced drug concentration of APRETUDE
- Refer to the full Prescribing Information for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during use of, and after discontinuation of APRETUDE; review concomitant medications during use of APRETUDE

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Table 3. Scenario Analysis Results^{2,7,12-14,19-21}

Scenario	Incremental cost per QALY gained
Base case ^a	\$46,843
PrEP use scenarios	
CAB-LA vs no PrEP	CAB-LA cost saving
Oral PrEP adherence (IDWeek 2021 RWE)	CAB-LA cost saving
Population subgroups	
Among MSM and TGW	\$61,074
Among Black MSM	CAB-LA cost saving
Among Hispanic MSM	\$84,438
Among White MSM	\$107,090
Among CGW	CAB-LA cost saving
Duration of HIV risk	
2 years	\$40,432
10 years	\$83,206

CAB-LA, cabotegravir long-acting; CGW, cisgender women; FTC/TAF, emtricitabine/tenofovir alafenamide; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality adjusted life years; RWE, real world evidence; TGW, transgender women.

^aBase-case analysis compared CAB-LA with FTC/TDF for the overall PrEP-eligible population over a 5-year duration of risk following the parameters outlined in the model overview and inputs and assumptions.

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IMPORTANT SAFETY INFORMATION FOR APRETUDE (cabotegravir) (CONTINUED)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 1\%$, all grades) with APRETUDE were injection site reactions, diarrhea, headache, pyrexia, fatigue, sleep disorders, nausea, dizziness, flatulence, abdominal pain, vomiting, myalgia, rash, decreased appetite, somnolence, back pain, and upper respiratory tract infection.

DRUG INTERACTIONS

- Refer to the full Prescribing Information for important drug interactions with APRETUDE
- Drugs that induce UGT1A1 may significantly decrease the plasma concentrations of cabotegravir

USE IN SPECIFIC POPULATIONS

- **Lactation:** Assess the benefit-risk of using APRETUDE to the infant while breastfeeding due to the potential for adverse reactions and residual concentrations in the systemic circulation for up to 12 months or longer after discontinuation
- **Pediatrics:** Not recommended in individuals weighing less than 35 kg

Please see Important Safety Information for APRETUDE throughout.

Please see accompanying full Prescribing Information, including Boxed Warning, for APRETUDE.

INTENDED FOR DISTRIBUTION ONLY TO PAYERS, FORMULARY COMMITTEES, OR SIMILAR ENTITIES.

