Protocol

Study ID: 223857

Official Title of Study: An observational study evaluating long-acting injectable cabotegravir (CAB-LA; Apretude) healthcare provider and user experience and utilization for pre-exposure prophylaxis (PrEP) against HIV in Canada

Date of Document: 06-Oct-2025

Ex. Protocol Final

NON-INTERVENTIONAL STUDY PROTOCOL

UNIQUE IDENTIFIER	CTMS ID: 223857
TITLE	An observational study evaluating long-acting injectable cabotegravir (CAB-LA; Apretude) healthcare provider and user experience and utilization for pre-exposure prophylaxis (PrEP) against HIV in Canada
STUDY ACCOUNTABLE PERSON	PPD Health Outcomes Scientist, GSK Canada
CONTRIBUTING AUTHORS	Dr. PPD, St. Michael's Hospital PPD, GSK Canada PPD, GSK Canada PPD, GSK Canada PPD, ViiV Healthcare PPD, ViiV Healthcare PPD, Broadstreet HEOR PPD, Broadstreet HEOR PPD, Broadstreet HEOR PPD, Broadstreet HEOR PPD, Broadstreet HEOR
ASSET ID	GSK1265744
ViiV ASSET	Cabotegravir (APRETUDE)
INDICATION	HIV Prevention
DATA COLLECTION TYPE	Multiple Methods; Primary and Secondary Data Collection (Cross-Sectional Survey, Retrospective Database Analysis)
SAFETY OBJECTIVE	YES

ASSET INVOLVEMENT	YES
TSS/PASS ASSESSMENT PERFORMED	YES
EVALUATING A PRODUCT **(TIER TYPE)**	Tier 1
REGULATORY COMMITMENT	YES

***Disclaimer**: This study is a Post-Authorization Safety Study (PASS) with two sets of objectives. The **primary objectives** address a Health Canada-mandated request, while the **secondary objectives**, which are not mandated by Health Canada, aim to provide insights into the real-world use of CAB-LA.*

Ex. Protocol Final

TITLE PAGE

Study ID: CTMS ID: 223857

Division: Health Outcomes, Pharma Research & Development

Information Type: Non-Interventional Study Protocol

Title: An observational study evaluating long-acting injectable cabotegravir (CAB-LA; Apretude) healthcare provider and user experience and utilization for pre-exposure prophylaxis against human immunodeficiency virus in Canada

Effective Date:

Author(s):

PPD (St. Michael's Hospital)

PPD (GSK)

PPD (GSK)

PPD (GSK)

PPD (ViiV Healthcare)

PPD (ViiV Healthcare)

PPD (Broadstreet HEOR)

PPD (Broadstreet HEOR)

PPD (Broadstreet HEOR)

PPD (Broadstreet HEOR)

PPD (Broadstreet HEOR)

Ex. Protocol Final

STUDY INFORMATION

Title	An observational study evaluating long-acting injectable cabotegravir (CAB-LA; Apretude) healthcare provider and user experience and utilization for pre-exposure prophylaxis (PrEP) against HIV in Canada
Medicinal product	Cabotegravir 200mg/ml extended release injectable suspension
INDICATION	Pre-exposure prophylaxis (PrEP)
Marketing authorisation holder(s)	ViiV Healthcare Canada
Country of study	Canada
Author	PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	VIIV Healthcare ULC 75, Rue Queen, Montreal, Quebec, H3C 2N6, Canada

Ex. Protocol Final

TABLE OF CONTENTS

PAGE

Ex. Protocol Final

LIST OF ABBREVIATIONS

AE	Adverse event
Apr	April
aRMM	Additional risk minimization measure
CAB-LA	Long-acting injectable cabotegravir (Apretude®)
CGW	Cisgender women
CI	Confidence interval
Dec	December
gbMSM	Gay, bisexual, and men who have sex with men
GSK	GlaxoSmithKline
GPP	Good Participatory Practice
HC	Health Canada
HCP	Healthcare provider
HEOR	Health Economics and Outcomes Research
HIV	Human immunodeficiency virus
HSI	Human Safety Information
IEC	Independent Ethics Committee
IHD	Individual Human Data
ID	Identification
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
IRBs	Institutional Review Boards
KAB	Knowledge, Attitude and Behaviour
LGBTQ	Lesbian, gay, bisexual, transgender or queer
MSM	Men who have sex with men
PDC	Proportion of days covered
PK	Pharmacokinetic
PrEP	Pre-exposure prophylaxis
PSP	Patient support program
REB	Research ethics board
Q	Question
QC	Quality control
QR	Quick response
Q2M	Every two months
Q2	Quarter two
Q3	Quarter three
Q4	Quarter four
REB	Research ethics board
SD	Standard deviation
TAF/FTC	Tenofovir alafenamide–emtricitabine combination (Descovy)
TBC	To be confirmed
TDF/FTC	Tenofovir disoproxil fumarate- emtricitabine combination (Truvada)
TGW	Transgender women
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States

Ex. Protocol Final

TRADEMARK INFORMATION

Trademarks of the <<GSK\ViiV>> group of companies	Trademarks not owned by the <<GSK\ViiV>> group of companies
APRETUDE	

Ex. Protocol Final

1.1. Sponsor Signatory

Title: An observational study evaluating long-acting injectable cabotegravir (CAB-LA; Apretude) healthcare provider and user experience and utilization for pre-exposure prophylaxis against human immunodeficiency virus in Canada

Compound Number: GSK1265744

Adeteju Ogunbameru, Health Outcomes Scientist, Study Accountable Person, GSK Canada	Date (DD Month YYYY)
Dominy Browning, Global Head, HEOR, ViiV Healthcare (On Behalf of Annemiek de Ruiter and Sherene Min, PRC Co-Chairs)	Date (DD Month YYYY)
Nassrin Payvandi, VP, Safety & Pharmacovigilance, ViiV Global Markets	Date (DD Month YYYY)
Jens Ulrich Stegmann **Qualified Person for Pharmacovigilance**	Date (DD Month YYYY)

Qualified Person for Pharmacovigilance (QPPV)/Delegate required for TSS/PASS – The QPPV signature box should be deleted if the study is not a PASS or TSS.

Ex. Protocol Final

Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name: Dr. Darrell Tan

Investigator Signature	Date (DD Month YYYY)

2. SYNOPSIS

Title

An observational study evaluating long-acting injectable cabotegravir (CAB-LA; Apretude) healthcare provider and user experience and utilization for pre-exposure prophylaxis against human immunodeficiency virus in Canada

Rationale and background

Long-acting cabotegravir (CAB-LA; Apretude), is the first and only long-acting injectable form of pre-exposure prophylaxis (PrEP) available in Canada and is indicated 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 human immunodeficiency virus (HIV)-1 infection. Health Canada (HC) has recommended the use of additional risk minimization measures (aRMMs) in the form of an Education Program (consisting of a Prescribers' Guide, Prescribers' Checklist, User Guide, and Injection Appointment Reminder Card) given the potential risk of HIV-1 seroconversion and drug resistance when using CAB-LA. A Knowledge, Attitude and Behaviour (KAB) study is needed to evaluate the effectiveness of these aRMMs and to support HC's commitment to meeting the 2030 Joint United Nations Programme on HIV/AIDS (UNAIDS) HIV global targets.[1]

Further, there is a need to assess real-world use of CAB-LA by evaluating the characteristics and experiences of Canadian healthcare providers (HCPs) and users, including utilization patterns, satisfaction and PrEP-related preferences, as well as understanding the decision-making process of HCPs who prescribe CAB-LA and users of CAB-LA. This real-world evidence will be valuable to supporting clinical decision-making in assessments of CAB-LA as a new option for PrEP users.

Research question and Objective(s)

The primary aim of this study is to evaluate the effectiveness of the aRMMs for CAB-LA within Canada, among HCPs and CAB-LA users, and include describing:

1. Whether HCPs and CAB-LA users have used aRMMs for CAB-LA (Prescribers' Guide, Prescribers' Checklist, User Guide, Injection Appointment Reminder Card);
2. HCP knowledge of key CAB-LA risk messages within the HCP-specific aRMMs (Prescribers' Guide and Prescribers' Checklist);
3. User knowledge of key CAB-LA risk messages within the user-specific aRMMs (User Guide and Injection Appointment Reminder Card);
4. HCP (prescribers') attitudes regarding the importance of selecting individuals who will adhere to the CAB-LA dosing schedule and attend follow-up visits; and
5. HCP and user behaviours as they relate to key CAB-LA risk messages within the aRMMs.

The secondary objectives are additional research objectives, not an HC-mandated requirement. The secondary objectives are to:

Among HCPs who prescribe or administer CAB-LA, describe:

1. Decision-making processes regarding the choice between oral PrEP and CAB-LA;
2. Experience implementing, prescribing, or managing CAB-LA and oral PrEP in clinical practice and among individuals eligible for PrEP, including HIV-testing;
3. Use of CAB-LA oral lead-in and oral bridging;
4. Management of pharmacokinetic (PK) tail among those who discontinue CAB-LA; and
5. Attitudes towards CAB-LA.

Among CAB-LA users, describe:

6. Demographic and clinical characteristics;
7. Decision-making processes regarding the choice between oral PrEP and CAB-LA.;
8. Experience using CAB-LA, including satisfaction and acceptability of the CAB-LA regimen, PrEP-related preferences, any benefits or limitations of HCP visit schedule, emotional and daily impact of using CAB-LA, and experience of stigma for using PrEP, including CAB-LA; and
9. Utilization patterns, including adherence and persistence, use of and acceptability of CAB-LA oral lead-in and oral bridging, rates of discontinuation, and reasons for discontinuation.

Study Design

This is an observational study, including the following sources of data and data collection time periods:

1. A cross-sectional survey of HCPs prescribing/administering CAB-LA and users of CAB-LA, to be conducted from December 2025 – April 2026; and
2. Retrospective analysis of CAB-LA user data in the Apretude Supports Patient Support Program [PSP] database, to be conducted from July 2024 – October 2027, with interim results in Q1/Q2 2026 and final results in Q4 2027.

Population

The study population includes a) HCPs comprised of physicians, nurses, and pharmacists who prescribe or administer CAB-LA b) users of CAB-LA 16 years of age or older (conditional based on Research Ethics Boards (REBs) granting a waiver of parental/guardian consent for participants under the age of majority in their province/territory; otherwise the study population will include users of CAB-LA 18 years of age or older).

Variables

Participants will be asked about individual characteristics, as well as their knowledge, attitudes, and practices toward CAB-LA (see research objectives). The full list of questions can be found in the surveys.

Data sources

Data sources will include the data collected through both the HCP and CAB-LA user surveys and the Apretude Supports Program database.

Study size

The target sample size is 100 HCPs for the HCP survey and 250 CAB-LA users for the CAB-LA user survey.

Data analysis

The study will primarily be descriptive and will use the R statistical software. The categorical data will be presented as frequencies and percentages. Continuous data will be presented as means with standard deviations and medians with interquartile ranges (IQR). The number and percentage of HCPs and CAB-LA users who have provided correct responses to at least 80% of all knowledge questions will be reported (target threshold for the study). Similarly, the number and percentage of HCPs and CAB-LA used who have provided responses indicative of optimal behaviour will be summarized for each question. We define optimal behaviour as how individuals act if they have understood and behaved in accordance with the key messages in the HCP- and user-specific aRMMs. Results will be presented overall for HCPs and CAB-LA users, as well as stratified by characteristics of interest. For both the survey and the retrospective analysis of the cohort data from the Apretude Supports Program, the characteristics of HCPs and CAB-LA users will be summarized as frequencies and percentages (categorical variables) or as means, SD, medians and ranges IQR (continuous variables). The survey questions will largely have categorical response options, which will be summarized as frequencies and percentages. The analysis of survey data will be guided by shell tables developed based on the final version of the survey. The retrospective analysis of the cohort data from the Apretude Supports Program used to understand utilization patterns will be summarized as frequencies and percentages (categorical variables) or medians and IQR (for continuous variables), guided by shell tables developed based on the data available from the Apretude Supports Program.

3. AMENDMENTS AND UPDATES

None

4. MILESTONES

Milestone	Planned date
Protocol Finalization & Approval	October 2025
Submission to relevant ethics committees	October 2025
Primary Objectives:	
Start of Data Collection:	December 2025

Milestone	Planned date
Cross-Sectional HCP & User Survey	
End of Data Collection: Cross-Sectional HCP & User Survey	April 2026
Final Results: Reported to Health Canada	June 2026
Secondary Objectives:	
Start of Data Collection: Cross-Sectional HCP & User Survey	December 2025
End of Data Collection: Cross-Sectional HCP & User Survey	April 2026
Interim Report: Interim PSP Data Analysis	May 2026
Final Results: Final PSP Data Analysis	November 2027

5. RATIONALE AND BACKGROUND

5.1. Background

Long-acting cabotegravir (CAB-LA; Apretude) is a human immunodeficiency virus (HIV)-1 integrase strand transfer inhibitor (INSTI) indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection among at-risk adults and adolescents aged 12 years and older and weighing at least 35 kg. It is administered as a single intramuscular injection by a healthcare provider (HCP) every two months (Q2M), following two initiation injections administered one month apart. To reduce the risk of drug resistance development among CAB-LA users with previously undetected HIV infection, individuals must be tested for HIV-1 infection prior to initiating CAB-LA and should be tested for HIV-1 infection with each subsequent CAB-LA injection. Oral cabotegravir tablets may also be used as an optional lead-in to assess tolerability, or as a short-term oral PrEP option for individuals who plan to miss doses with CAB-LA.

PrEP is recommended as an effective HIV prevention strategy among several groups at risk of HIV infection, including men who have sex with men (MSM) and transgender women (TGW) who report sexual behaviours associated with increased risk of HIV infection, heterosexually active persons who have sex with partners at high risk of HIV infection, and persons who inject drugs.[2,3]

In Canada, there are two oral PrEP options available, tenofovir disoproxil fumarate-emtricitabine combination (TDF/FTC; brand name: Truvada) and tenofovir alafenamide–emtricitabine combination (TAF/FTC; brand name: Descovy).[4] These oral options are taken once daily. TDF/FTC may also be taken on demand with the following regimen: 2 pills 2-to-24 hours before sex, followed by 1 pill after 24 hours, and another pill after 24 hours of the second pill (2-1-1 dosing).[5] The effectiveness of PrEP depends on key

behavioural factors, such as medication adherence and patient participation in routine clinical follow-up.[6-11] A systematic literature review summarizing the effectiveness of PrEP in clinical trials found PrEP effectiveness was highest compared to placebo (risk ratio = 0.30, 95% confidence interval: 0.21-0.45, P < 0.001) when PrEP adherence was more than 70%.[12] Conversely, trials with low adherence to PrEP did not show a significant protective effect.[12] Real-world evidence on PrEP effectiveness using data from the French national health care system between 2016 and 2020 (N=46,706 individuals), has shown that PrEP effectiveness was 60% (95% confidence interval [CI] 46 to 71) overall, 93% (84 to 97) for high PrEP adherence, and 86% (78 to 92) if excluding periods after PrEP discontinuation.[13] PrEP effectiveness in this study was significantly reduced in individuals with certain demographics (<30 years old and socioeconomically deprived), both of which have also showed low levels of PrEP adherence and high rates of PrEP discontinuation.[13]

In February 2024, Canada reiterated its commitment[14] to meeting the Joint United Nations Programme on HIV/AIDS (UNAIDS) global targets for HIV testing and treatment[1] which included having 95% of people living with HIV diagnosed, 95% of those diagnosed on treatment; and 95% of those on treatment having a suppressed viral load. This commitment is timely, given that HIV surveillance in Canada in 2023[15] indicated a 35.2% increase in HIV diagnoses between 2022 and 2023, bringing the national incidence rate of HIV to 6.1 per 100,000 population. Across the provinces, Saskatchewan and Manitoba (19.4 and 19.3 per 100,000 respectively) had the highest rates of HIV diagnoses, while the Atlantic provinces (2.4), territories (2.2) and British Columbia (3.3) had the lowest.[15] Additionally, new HIV diagnoses in males are more than double those in females (8.1 vs 3.9 per 100,000) and the highest among those aged 30 to 39 years (14.3 per 100,000).[15]

The uptake of oral PrEP in Canada has steadily increased over time. An analysis conducted between 2014 and 2018 showed a 21-fold increase in the number of PrEP users across eight Canadian provinces from 460 in 2014 to 9,657 in 2018.[16] This uptake remained consistent between 2019 and 2022, where the average PrEP use across nine Canadian provinces has increased each year from 61 (in 2019) to 89 per 100,000 people (in 2022).[17]

Despite improved awareness of PrEP and consistent uptake over the years, PrEP use remains far below guideline recommendations. A recent study that estimated the number and characteristics of PrEP users in Ontario, 2015 – 2018, found a 713% increase, from 374 users in 2015 quarter three (Q3) to 3041 users in 2018 quarter two (Q2).[18] However, this number is still below the total number of individuals in Ontario who meet the Canadian guideline recommendations for PrEP use, estimated at > 30,000 for gay, bisexual, and men who have sex with men (gbMSM) alone.[2,19]

Differences in PrEP uptake by key demographics have remained consistent over time. Between 2014 and 2018, PrEP use increased in both sexes, but more substantially among males (23-fold) than females (five-fold).[16] These differences remained in 2022, where 98% of PrEP was used by males.[17] Differences in PrEP uptake also varied by provinces.[17] An analysis across nine provinces showed estimated annual PrEP use prevalence in 2022 was the highest in British Columbia (132 per 100,000 people) and lowest in Newfoundland and Labrador (26 per 100,000 people).[17] When analysed by age, PrEP use in 2022 was the highest among those aged 30–39 years of age.[17]

The insufficient uptake of oral PrEP when compared to Canadian guideline recommendations, in addition to significant variations by factors such as sex, age, and jurisdiction, highlight unmet needs and gaps in HIV prevention. These consistent differences could be influenced by stigma and adherence challenges associated with current options.[20,21] In early qualitative analyses from the 'first wave' of PrEP users among 16 men in Toronto, sex-stigma emerged as a complex theme overlapping three domains: 1) PrEP-related stigma, 2) PrEP as a perceived tool for combating HIV-related stigma, and 3) PrEP as illuminating structural stigma.[20] A more recent cross-sectional survey aimed to explore the association between PrEP-related stereotypes and perceived disapproval (i.e., PrEP-related stigma) and PrEP use among adult gbMSM in Ontario and British Columbia. This survey found that PrEP-related stigma was associated with not using PrEP, particularly with PrEP discontinuation.[21] These findings provide further evidence that stigma remains a barrier to PrEP use.[21] Thus, there is a need for options that are convenient to individuals and that promote adherence. In particular, the panel responsible for Canadian guidelines for HIV PrEP emphasizes the importance of increasing access, reducing barriers to implementation, and diversifying approaches to PrEP.[22]

CAB-LA was approved by Health Canada (HC) in May 2024 and is the first and only long-acting injectable PrEP option available in Canada. HC approval was based on the results of two key phase IIb/III trials (HPTN 083 and HPTN 084), which evaluated the safety and efficacy of CAB-LA for PrEP in MSM, TGW, and cisgender women (CGW) at increased risk of acquiring HIV.[23,24]

In late 2024, the panel responsible for Canadian guidelines for PrEP considered CAB-LA appropriate for use for the prevention of sexually acquired HIV infection, based on efficacy, safety, and tolerability data. Specifically, the updated guidelines included a strong recommendation of CAB-LA for HIV-negative cisgender men and TGW where the risk of HIV acquisition is related to sex with cisgender men as well as HIV-negative CGW where risk of HIV acquisition is related to heterosexual activity. The panel further recommended CAB-LA as a PrEP option for HIV-negative cisgender men where the risk of HIV acquisition is related to heterosexual activity.

The use of CAB-LA reduces the number of doses needed for effective HIV prevention from daily pills to as few as six injections per year. This simplified dosing schedule may contribute to the observed superiority of CAB-LA compared to daily oral PrEP use in clinical trials (69% and 90% lower rates of HIV acquisition reported in HPTN 083 and HPTN 084, respectively).[25,26] While this first and only long-acting injectable PrEP option in Canada may address important barriers to adherence of PrEP, understanding preferences, patterns of use, attitudes, and opinions will provide key insights into how HCPs and users engage with CAB-LA in the real world, and guide strategic decisions to effectively expand adoption and maximize impact on HIV prevention.

5.2. Rationale

The phase IIb/III trials, HPTN 083 and HPTN 084, which led to HC approval of CAB-LA, demonstrated that it was highly effective in preventing HIV. However, seroconversions still occurred, with 12 cases in HPTN 083 and 3 in HPTN 084.[27,28] These infections arose

at different stages of use—some while receiving on-time CAB-LA injections, others more than six months after the last dose, and some during the oral lead-in phase.[29] In certain cases, integrase strand transfer inhibitor (INSTI) resistance mutations developed, particularly Q148R, E138K, and G140S, which are known to reduce susceptibility to CAB-LA. The clinical impact of these mutations is significant, as resistance can limit future treatment options, making it more difficult to control HIV with standard first-line therapies. Additionally, because CAB-LA is a long-acting injectable, resistance could still develop after stopping the drug if undiagnosed HIV is present.

Due to the risk of drug resistance with use of CAB-LA in undiagnosed HIV-1 infection, HC requested the use of additional risk minimization measures (aRMMs) in the form of an Education Program (consisting of a Prescribers' Guide, Prescribers' Checklist, User Guide and Injection Appointment Reminder Card) to be implemented for HCPs prescribing and administering CAB-LA and CAB-LA users. The Prescriber Guide contains information regarding use of CAB-LA as an overall HIV-1 infection prevention strategy and optimal use of CAB-LA providing detail on potential risks, consideration of alternative forms, importance of counselling, recommendations for ensuring adherence and dosing regiments, and suggestions for when doses are missed. The Prescribers Checklist details the list of reminders HCPs should discuss with CAB-LA users at initial and follow-up visits, including reminders for evaluation, counselling, checking clinical symptoms, and adherence. The User Guide relays important information to individuals at risk of HIV infection regarding what they need to know prior to starting, when taking and when discontinuing CAB-LA. The Injection Appointment Reminder Card provides details regarding date of injection visit, importance of strict adherence, and the emergency contact information in case of troublesome symptoms and side effects. The aRMMs are available primarily online at the Apretude Resource Portal website available in English and French.[30,31]

These aRMMs have distinct key risk messages which include 1) CAB-LA should be used as part of a comprehensive prevention strategy; 2) there is potential risk of HIV-1 drug resistance development in individuals with undiagnosed HIV-1 infection; 3) strict adherence to the recommended dosing schedule is important to reduce risk of HIV-1 infection and the potential development of resistance and 4) regular monitoring and testing is needed to confirm HIV-1 status prior to starting and during CAB-LA use.

Per HC's request, a Knowledge, Attitude and Behaviour (KAB) study is needed to evaluate the effectiveness of these aRMMs based on pre-defined success thresholds for knowledge and behaviour among this population regarding key risk messages.

In addition to the KAB study requested by HC, this study also aims to collect real-world data in Canada by describing the characteristics and experiences of Canadian HCPs and users, and understanding the decision-making processes of HCPs and individuals eligible for PrEP. Indeed, existing data gaps include reasons for PrEP use and specifically why CAB-LA was selected, utilization patterns (adherence and persistence), CAB-LA user satisfaction and PrEP-related preferences, as well as understanding the decision-making processes of HCPs who prescribe CAB-LA and users of CAB-LA.

Further, it is important to understand variation in real-world usage of CAB-LA, including use of oral lead-in and oral bridging to prevent missed doses, as well as how the pharmacokinetic (PK) tail is managed among users who discontinue CAB-LA. These data will improve understanding of the appropriateness of CAB-LA use among those who are eligible for PrEP and the need for tailored safety messaging regarding use of oral CAB-LA. From the user perspective, it is important to understand the impact of CAB-LA on their daily life, including perspectives regarding stigma associated with the use of PrEP, the impact of the dosing regimen on daily activities and reasons for discontinuing CAB-LA. The user-voice is an important perspective to capture to help improve the PrEP experience for users, which will drive better rates of initiation and adherence to PrEP for individuals at risk of HIV infection. In particular, understanding the CAB-LA user experience, including satisfaction and preferences, and their perceptions of judgement associated with PrEP and CAB-LA use, may provide valuable insights into how CAB-LA may help to fill existing gaps within the HIV prevention landscape.

Although this research need is not an HC-mandated requirement, real-world evidence from this study will be valuable in informing and supporting the clinical and broader public health decision-making process for CAB-LA in Canada. Specifically, understanding users' reasons for CAB-LA use, their satisfaction and preferences can be valuable to clinicians in counselling users, as well as for raising awareness in the community. Understanding utilization patterns may further help inform public health and programmatic decisions about population coverage, and, understanding the decision-making process of HCPs who prescribe CAB-LA and users of CAB-LA can help inform the design of future educational programs. Together, this information can help drive Canada towards our HIV prevention goals.

6. RESEARCH QUESTION AND OBJECTIVE(S)

6.1. Primary Objectives

The primary aim of this study is to evaluate the effectiveness of the aRMMs for CAB-LA within Canada, specifically addressing HC's request. More specifically, the primary objectives are to evaluate:

1. Whether HCPs and CAB-LA users have used aRMMs for CAB-LA (Prescribers' Guide, Prescribers' Checklist, User Guide, Injection Appointment Reminder Card);
2. HCP knowledge of key CAB-LA risk messages within the HCP-specific aRMMs (Prescribers' Guide and Prescribers' Checklist);
3. User knowledge of key CAB-LA risk messages within the user-specific aRMMs (User Guide and Injection Appointment Reminder Card);
4. HCP (prescribers') attitudes regarding the importance of selecting individuals who will adhere to the CAB-LA dosing schedule and attend follow-up visits; and
5. HCP and user behaviours as they relate to key CAB-LA risk messages within the aRMMs.

6.2. Secondary Objectives

The secondary objectives are additional research objectives, not an HC-mandated requirement. The secondary objectives are to:

Among HCPs who prescribe or administer CAB-LA, describe:

1. Decision-making process regarding the choice between oral PrEP and CAB-LA;
2. Experience implementing, prescribing, or managing CAB-LA and oral PrEP in clinical practice and among individuals eligible for PrEP, including HIV-testing;
3. Use of CAB-LA oral lead-in and oral bridging;
4. Management of PK tail among those who discontinue CAB-LA; and
5. Attitudes towards CAB-LA.

Among CAB-LA users, describe:

6. Demographic and clinical characteristics;
7. Decision-making process regarding the choice between oral PrEP and CAB-LA;
8. Experience using CAB-LA, including satisfaction and acceptability of the CAB-LA regimen, PrEP-related preferences, any benefits or limitations of HCP visit schedule, emotional and daily impact of using CAB-LA, and experience of stigma for using PrEP, including CAB-LA; and
9. Utilization patterns, including adherence and persistence, use of and acceptability of CAB-LA oral lead-in and oral bridging, rates of discontinuation, and reasons for discontinuation.

7. RESEARCH METHODS

7.1. Study Design

This is an observational study consisting of cross-sectional surveys and a retrospective database analysis based on the study objectives outlined above.

Primary Objectives

A cross-sectional survey will be conducted among HCPs and CAB-LA users and will involve primary data collection (KAB survey). The KAB survey will be conducted at one time point corresponding to 18-months +/- 2-month post CAB-LA launch (July 15, 2024), with data collection occurring from December 2025 to April 2026. As the survey is cross-sectional, there will be no follow-up surveys, i.e., no pre-index or post-index follow-up data will be collected. The data collection start date for the KAB survey will be dependent on the final protocol approval date by HC, and may occur later (i.e., between January 2026 to May 2026).

Secondary Objectives

For the secondary objectives 1 through 8, primary data will be collected through surveys administered to HCPs and CAB-LA users (see Table 1). The HCP and user surveys will be conducted at one time point corresponding to approximately 18-months +/- 2-month post CAB-LA launch (December 2025 to April 2026).

For secondary objectives 6 and 9 a retrospective cohort analysis will be executed using data from the CAB-LA patient support program ("Apretude Supports Program") database (Table 1), which captures basic CAB-LA use information for all individuals enrolled in the program. In the Apretude Supports Program database, data will be included for individuals initiating CAB-LA between 15 July 2024 (the date of commercial availability in Canada) and October 2026 (the ascertainment period). Within this ascertainment period, eligible individuals will be indexed into the cohort at the date of initiation of CAB-LA injections. An ascertainment period end date of October 2026 was chosen to allow for a minimum 1-year follow-up from initiation of CAB-LA (index date) given final analysis will take place November 2027. An interim analysis is planned for Q1/Q2 2026 for data available up to that time point (July 2024 to Q1/Q2 2026).

Two separate sources of CAB-LA user demographic data will be available in this study to address secondary objective 6: one from the CAB-LA user survey and one from the Apretude Supports Program database. If linkage between the survey data and PSP database is feasible, the analysis will aim to combine the data to gain further insights particularly in regards to user factors impacting utilization patterns. The CAB-LA user survey data will be used to explore relationships between demographic characteristics and objectives 7 and 8, while the Apretude Supports Program data will inform analyses related to objective 9.

Table 1. Study objectives and data collection matrix

Secondary objectives		Primary data collection		Secondary data collection
		HCPs survey	CAB-LA users survey	Retrospective Cohort Data Analysis (from Apretude Supports Program)
1	Decision-making process regarding the choice between oral PrEP and CAB-LA	X		
2	Experience implementing, prescribing, or managing CAB-LA and oral PrEP in clinical practice and among individuals eligible for PrEP, including HIV-testing	X		

3	Use of CAB-LA oral lead-in and oral bridging	X		
4	Management of PK tail among those who discontinue CAB-LA	X		
5	Attitudes towards CAB-LA	X		
6	Demographic and clinical characteristics		X	X
7	Decision-making process regarding the choice between oral PrEP and CAB-LA		X	
8	Experience using CAB-LA, including satisfaction and acceptability of the CAB-LA regimen, PrEP-related preferences, any benefits or limitations of HCP visit schedule, emotional and daily impact of using CAB-LA, and experience of stigma for using PrEP, including CAB-LA		X	
9	Utilization patterns, including adherence and persistence, use of and acceptability of CAB-LA oral lead-in and oral bridging, rates of discontinuation, and reasons for discontinuation			X

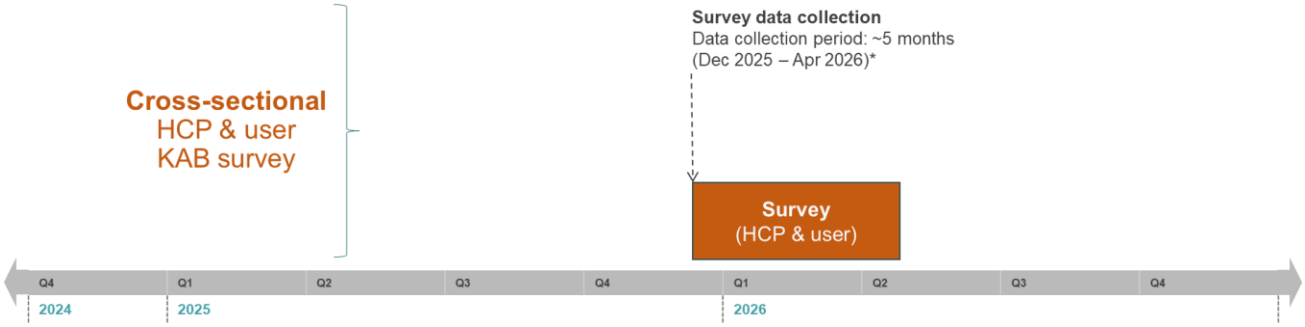
7.1.1. Study Schematic

Primary Objectives

The survey will address the five primary objectives. A study design schematic is shown in Figure 1.

Figure 1. Study schematic for cross-sectional HCP and user survey

Ex. Protocol Final



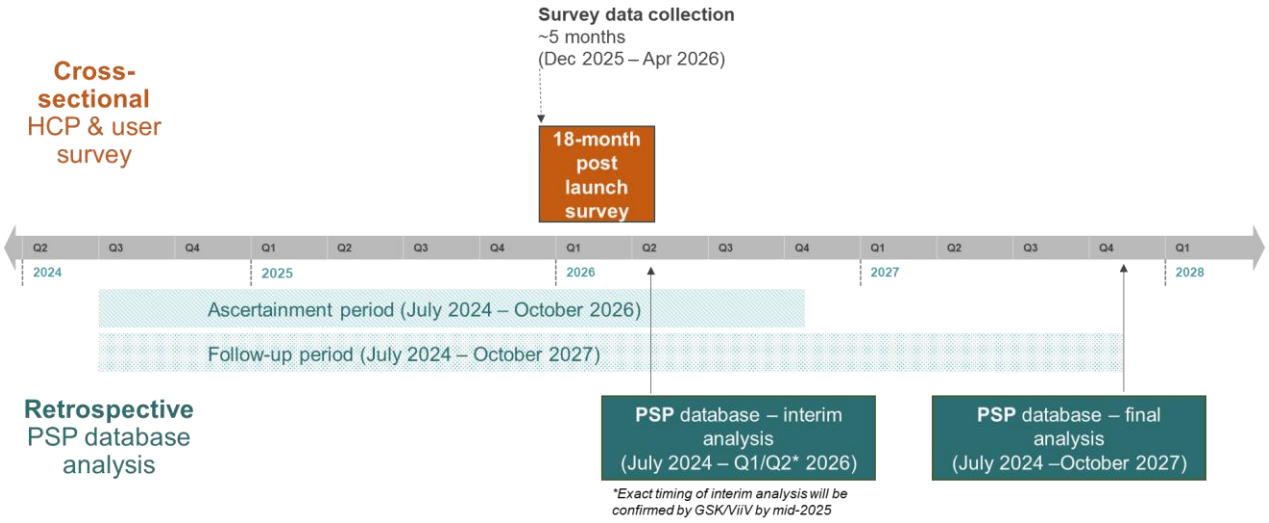
Abbreviations: Apr, April; Dec, December; HCP, Healthcare provider.

*Exact timing of data collection will be adjusted based on Health Canada protocol review timelines

Secondary Objectives

The survey will address secondary objectives 1-8 (Figure 2). The retrospective database analysis will address secondary objectives 6 and 9 (Figure 3).

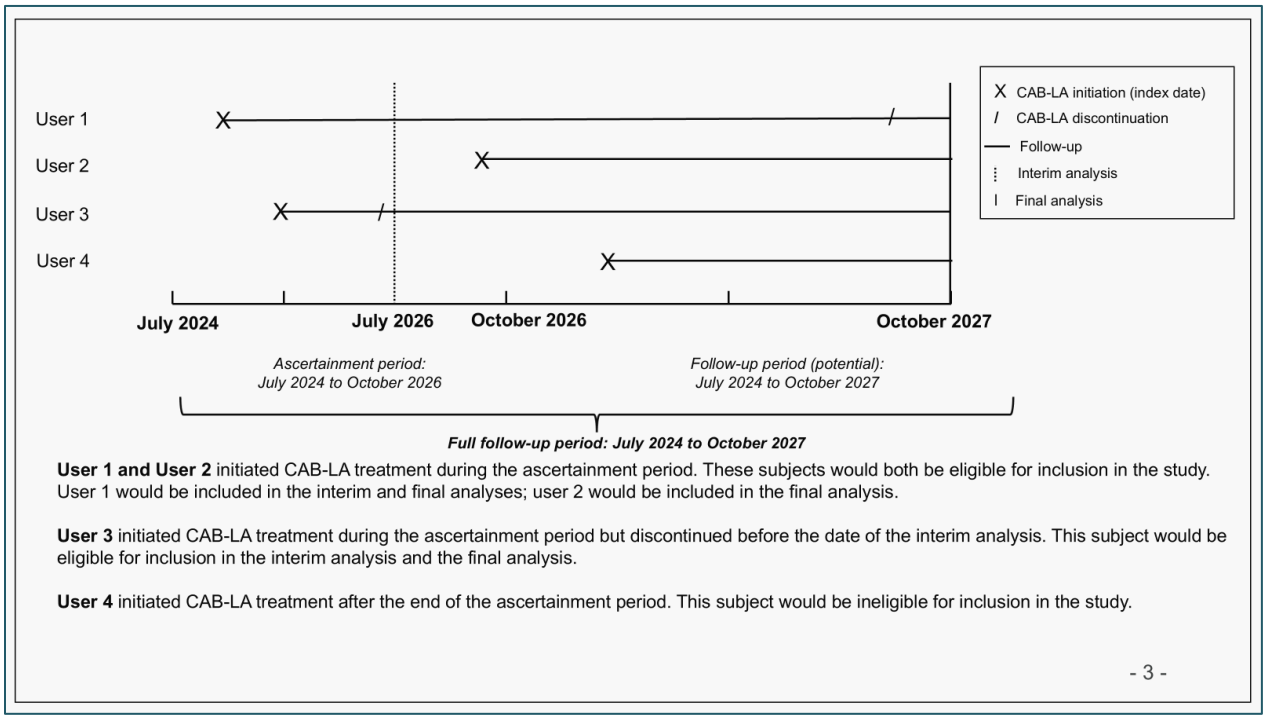
Figure 2. Study schematic for secondary objective survey and retrospective database analysis



Abbreviations: Apr, April; Dec, December; HCP, Healthcare provider; PSP, Patient support program.

Figure 3. Study schematic for retrospective database analysis (Apretude Supports Program)

Ex. Protocol Final



Abbreviations: CAB-LA, Long-acting injectable cabotegravir

7.2. Study Population and Setting

HCPs

The HCP study population will comprise physicians, nurses, and pharmacists who prescribe CAB-LA or who manage CAB-LA use among CAB-LA users in Canada. For example, not all nurses and pharmacists are able to prescribe CAB-LA (some may be able to prescribe by way of a medical directive); however, these HCPs may still have experience administering CAB-LA and managing care of CAB-LA users. For questions specific to prescribing decisions, the question will only be asked of prescribers.

CAB-LA Users

For the survey component of the study, CAB-LA users will be recruited from different clinical settings where they access PrEP (for example, but not limited to hospitals, outpatient clinics, and pharmacies) across Canada. For the retrospective database analysis, data from the Apretude Supports Program will be used. Due to the logistical barrier of research ethics boards (REB) typically requiring parental/guardian consent in order for minors to participate in research, adolescent CAB-LA users (≥16 years of age) may experience barriers to participation in the survey driven by fears about parent/guardian access to sensitive information, their potential disapproval, and interpretation of their participation as being sexually active or lesbian, gay, bisexual, transgender or queer (LGBTQ); fear of being 'outed', stigmatized, or punished by their families.[38-40] Thus, a waiver of parental/guardian consent will be requested with the appropriate REBs in order to reduce such barriers to adolescent participation. If the waiver is granted, adolescent

CAB-LA users will be considered for inclusion in the survey component. Otherwise, CAB-LA users must be at least 18 years of age in order to be considered for inclusion in the survey component. For the retrospective data analysis, users of all ages will be considered for inclusion.

Setting

For the survey component of the study, the setting will be web-based (online). For the retrospective analysis, the study setting will include various Apretude Supports Program sites across Canada: As of April 21, 2025, there are 159 sites across Canada, with sites distributed between Ontario (78), Quebec (40), British Columbia (15), Alberta (9), New Brunswick and Saskatchewan (5 each), Manitoba and Nova Scotia (2 each), and one site each in Newfoundland and Labrador, Prince Edward Island, and the Northern Territories. The Apretude Supports Program is designed to facilitate access and provide assistance to qualifying individuals who have been prescribed CAB-LA. The services under the program may include reimbursement investigation and/or financial assistance, assistance with drug administration, medication dispensing, medication delivery or testing, and disease and medication resources. This Program is a ViiV initiative and is administered by third-party service providers, specifically Bayshore Speciality Rx Ltd, selected by ViiV.

7.2.1. Eligibility Criteria

7.2.2. Inclusion Criteria

HCP KAB Survey

To be eligible for participation in the study, HCPs must:

- Be a physician, nurse or pharmacist;
- Be able to independently complete the survey in English or French; and
- Meet one of the following criteria outside of a clinical trial setting:
    - Have prescribed CAB-LA for HIV PrEP in Canada; or
    - Have administered CAB-LA for HIV PrEP in Canada; or
    - Have been or are currently involved in some aspect of CAB-LA management for HIV PrEP in Canada.

User KAB Survey

To be eligible for participation in the study, individuals must meet all the following criteria:

- Provide a signed and dated informed consent form for participation in this research study;
    - Be capable of providing informed consent;
- Be at least 16 years of age at the time of consent into the study;
- Must be able to independently complete the survey in English or French; and
    - Have received at least one injection of CAB-LA for HIV PrEP.

Apretude Supports Program Database Analysis

To be eligible for inclusion in the study, individuals within the Apretude Supports Program database must meet all of the following criteria:

- Evidence of a personally signed and dated informed consent document (i.e., Apretude Supports Program patient enrolment form) consenting to program analysis; and
- Have received at least one injection of CAB-LA (with or without the optional lead-in treatment), with the first injection taking place between July 2024 and October 2026.

7.2.3. Exclusion Criteria

HCP KAB Survey

HCPs meeting any of the following criteria will be excluded from the study:

- Physicians, nurses or pharmacists in training.

User KAB Survey

Individuals meeting any of the following criteria will be excluded from the study:

- Participation in a clinical study that may interfere with participation in this study (i.e., clinical studies assessing the efficacy of long acting injectables for PrEP), during the study period.

Apretude Supports Program Database Analysis

Individuals within the Apretude Supports Program database meeting any of the following criteria will be excluded from the study:

- Initiated CAB-LA outside of the Apretude Supports Program (i.e., with a lack of historical data on CAB-LA injection dates prior to entry in the PSP).

7.3. Variables

7.3.1. Exposure Definitions

HCP Survey

For HCPs, exposure will be defined as having prescribed or managed use of CAB-LA for the prevention of HIV-1 among individuals at high risk in Canada eligible for CAB-LA based on the HC indication.

User Survey

For CAB-LA users, exposure will be defined as having previously initiated CAB-LA for the prevention of HIV-1. In the survey, this is defined as having received at least one dose of CAB-LA at the time of survey enrolment.

Apretude Supports Program Database Analysis

For CAB-LA users, exposure will be defined as having initiated CAB-LA for the prevention of HIV-1. In the Apretude Supports Program database analysis, this is defined as enrollment and initiation of CAB-LA through the Apretude Supports Program within the ascertainment period (i.e., have received at least one injection of CAB-LA, with the first dose taking place between July 2024 and October 2026). Data will be included for users until the end of the follow-up period (October 2027) or until discontinuation.

7.3.2. Outcome Definitions

The following characteristics and outcomes will be assessed to meet both the primary and secondary objectives for the study. For the HCP and user surveys, the following data will be collected at the time of survey completion, as well as any prior historic data. The time point for survey data collection will be from December 2025 to April 2026 for the primary and secondary objectives.

The HCP and user surveys are included in Annex 2, and the variables included in the Apretude Supports Program are included in Annex 1.

Demographic and clinical characteristic variables:

Table 2. Demographic and clinical characteristics included in the HCP survey

HCP Survey
• Age
• Gender identity
• Sex
• Province or territory of practice
• Type of HCP (e.g., physician, nurse, pharmacist) and HCP specialty (e.g., general practitioner, infectious disease specialist)
• Prescriber status
• Prior training in infectious disease and/or HIV medicine
• Practice setting/type (e.g., hospital, outpatient clinic, pharmacy, family health clinic)
• Years of practice in current role

• Years/months of experience with oral PrEP
• Experience working with CAB LA
• Number of CAB-LA users seen in practice per year
• Receipt of information on the use of CAB-LA through a ViiV representative

Table 3. Demographic and clinical characteristics included in the user survey

User Survey
• Age
• Sex (assigned at birth)
• Gender identity
• Sexual orientation
• Race
• Province or territory of residence
• Population density (urban vs. rural)
• Marital status
• Educational attainment
• Employment status
• Household income level
• Drug/substance use, alcohol use, smoking status
• Types of sexual activity
• Number of sexual partners
• Risks in the past 6 months that are related to: o Engagement in sex work o Getting diagnosed with a sexually transmitted infection o Injection of non-prescribed drugs e.g., heroin, fentanyl, methamphetamine o Use of non-injectable sex-enhancing drugs not prescribed by an HCP o Having a sex partner with HIV with an unknown or undetectable viral load

Table 4. Demographic and clinical characteristics included in the Apretude Supports Program database analysis (as data availability permits)

Apretude Supports Program database analysis
• Use of oral lead-in
• Number of injections received to-date
• Number of oral bridges, type of oral bridging used

Outcome Variables – Primary Objective

The HCP and user surveys will collect data on HCP and user access to the relevant aRMMs, as well as their knowledge and behaviours related to the key risk messages within the aRMMs. Additionally, the HCP survey will collect data on HCP attitudes related to the key risk messages with the relevant aRMMs. These risk messages are:

- CAB-LA should be used as part of a comprehensive prevention strategy;
- There is potential risk of HIV-1 drug resistance development in individuals with undiagnosed HIV-1 infection
- Strict adherence to the recommended dosing schedule is important to reduce risk of HIV-1 infection and the potential development of resistance and;
- Regular monitoring and testing are needed to confirm HIV-1 status prior to starting and during CAB-LA use

Definitions of outcome variables as follows:

- **Access** will be defined as the HCP or user having accessed and used the aRMM, to be assessed as the percentage of respondents who accessed and used the relevant aRMM.
- **Knowledge** will be defined as awareness and understanding of key CAB-LA risk messages within the relevant aRMMs for HCPs and users, to be assessed as a score based on the proportion of correct responses to knowledge-related questions specific to each risk message.
- **Attitude (HCP prescribers only)** will be defined as the perceived importance of carefully selecting individuals who will adhere to the CAB-LA regimen, in deciding to whom CAB-LA will be recommended. This will be assessed as the percentage of HCPs whose responses indicate agreement on the importance of this.
- **Behaviours** will be defined as performing the recommended actions outlined in the HCP and user aRMMs, as they relate to key CAB-LA risk messages. This will be assessed as a score based on the proportion of optimal behaviour responses to behaviour-related questions. This section will not assess use of the specific aRMMs, rather the behaviours related to the risk messages as described in the aRMMs.

Further details on outcomes assessment and analysis are provided below.

HCP Survey

From the HCP survey, data will be collected on:

Table 5. Outcome assessment areas in HCP survey

Domain	Subdomain	Survey Topic
Experience with prescriber aRMMs	Prescribers' Guide / Checklist / Reminder Card*	• Prior access to aRMM
Knowledge	Comprehensive HIV-1 infection prevention strategy	• Knowledge of additional prevention strategies
	Risk of developing drug resistance	• Knowledge of risk of developing resistance to CAB-LA if user acquires HIV-1 before or while taking CAB-LA or following discontinuation of CAB-LA • Steps to take with suspected or confirmed HIV-1 infection in CAB-LA user • Knowledge of the presence of residual concentrations of CAB-LA following discontinuation • Steps when user discontinues CAB-LA; considering alternative forms of PrEP for those at risk of HIV-1 infection
	Importance of CAB-LA adherence	• Knowledge of the importance of careful selection of individuals who agree to the CAB-LA dosing schedule • Knowledge of appropriate use of oral cabotegravir including for bridging • Steps when user misses oral cabotegravir dose or an injection appointment
	Regular monitoring/HIV-1 seroconversion	• Knowledge of testing requirements for HIV-1 infection prior to initiating CAB-LA, and with each subsequent injection of CAB-LA
Attitudes	Importance of CAB-LA adherence (prescribers only)	• HCP prescribers' perspective on the ideal adherence patterns for individuals being considered to receive CAB-LA

Domain	Subdomain	Survey Topic
Behaviours	Comprehensive HIV-1 infection prevention strategy (prescribers only)	• Frequency of counseling on additional prevention strategies • Frequency of counseling on use of the User Guide and Patient Medication Information to gain more information
	Risk of developing drug resistance	• HIV-1 status confirmation prior to prescribing CAB-LA and throughout use (prescribers only) • Frequency of counseling on steps if individual has suspected or confirmed HIV (prescribers only) • Frequency of counseling on alternative forms of PrEP among individuals considering discontinuation of CAB-LA (prescribers only) • Frequency of commencing antiretroviral therapy or referring for HIV treatment among individuals with suspected or confirmed HIV-1 diagnoses
	Importance of CAB-LA adherence (prescribers only)	• Frequency of carefully selecting individuals who will adhere to the CAB-LA dosing schedule prior to prescribing • Frequency of counseling on importance of adherence to dosing schedule • Frequency of counseling on booking next appointments
	Regular monitoring/HIV-1 seroconversion	• Frequency of risk assessment and HIV-1 testing (prescribers only) • Frequency of counseling on importance of regular HIV screening (prescribers only) • Steps taken when user misses a scheduled injection visit (not part of KAB scoring)
	Management of those with suspected or confirmed HIV	• Steps taken for suspected/confirmed HIV

* The question in the HCP survey about the Reminder Card specifically asks if the HCP or any member of their care team has ever accessed the Apretude Injection Appointment Reminder Card, which they provide to Apretude users (this question is not scored, it is

only included to better understand HCPs' general experience of accessing Apretude aRMMs).

The full list of variables for the HCP primary objective survey are available in Annex 2.

User survey

From the user survey, data will be collected on:

Table 6. Outcome assessment areas in user survey

Domain	Subdomain	Survey Topic
Experience with user aRMMs	User Guide / Reminder Card	• Prior access to aRMM • Mode of access to aRMM • Perceived ease of access to aRMM • Use of aRMM • Perceived usefulness of aRMM ▪ Reasons for not using aRMM, if applicable
Knowledge	Comprehensive HIV-1 infection prevention strategies	• Knowledge of susceptibility to HIV infection while on CAB-LA • Measures to be taken to further reduce risk of HIV infection while on CAB-LA • Knowledge of recommendation to consult with HCP when stopping CAB-LA
	Risk of developing drug resistance	• Knowledge of whether CAB-LA can be used if infected with HIV or with unknown HIV infection status • Knowledge of ways to reduce risk of getting HIV/developing resistance • Knowledge that CAB-LA will remain in the body for up to one year from last injection
	Importance of CAB-LA adherence	• Knowledge of CAB-LA dosing schedule including oral use (if applicable) • Risks of not being adherent • What to do in case of a missed injection
	Regular monitoring/HIV-1 seroconversion	• Knowledge of HIV testing recommendations before and during CAB-LA use

Domain	Subdomain	Survey Topic
Behaviours	Comprehensive HIV-1 infection prevention strategies	• Discussions with HCPs regarding prevention strategies • Use of additional prevention strategies including condom use and, not needle sharing • Actions taken when stopping CAB-LA
	Risk of developing drug resistance	• Actions taken when stopping CAB-LA (among users who have stopped CAB-LA)
	Importance of CAB-LA adherence	• Frequency of attending planned appointments

The full list of variables for the user primary objective survey are available in Annex 2.

Outcomes Assessment – Primary Objectives

For the primary objectives:

- Access of aRMMs will be assessed as the percentage of HCPs and users who accessed and read or used the materials.
- Knowledge outcomes will be assessed to summarize the level of correct or appropriate responses for individual questions and for individual HCPs and CAB-LA users. The proportion of correct responses to individual questions will be assessed across HCPs and CAB-LA users, as well as the proportion of correct responses among individual HCPs and CAB-LA users across all knowledge questions.
- As there is only one question for the attitude domain (for HCPs only), the proportion of HCPs with desirable attitude will be reported.
- Behaviour outcomes will be assessed to summarize the level of desirable or appropriate responses for individual questions and for individual HCPs and CAB-LA users. Most behaviour questions have Likert scale response option, in recognition that behaviour is typically observed on a continuum. Therefore, the response options that are somewhat optimal (e.g., “I sometimes provide counseling”) will be reported separately from the most optimal behaviour. The proportion of optimal and somewhat optimal responses to individual questions will be assessed across HCPs and CAB-LA users, as well as the proportion of both optimal and somewhat optimal responses among individual HCPs and CAB-LA users to all questions under each relevant risk message category and across all behaviour questions.

The survey questions that will elicit knowledge, attitude or behaviours, by risk message category are presented in Table 7.

Table 7. Survey questions categorization by risk message category

Risk Message Topic	User Survey		HCP Survey		
	Knowledge	**Behaviour**	**Knowledge**	**Attitude**	**Behaviour**
Comprehensive prevention strategy	Q31, Q32, Q38	Q47, Q48, Q49	Q13		Q30, Q33
Risk of developing drug resistance	Q36,Q37, Q39, Q40	Q51	Q15, Q16, Q17, Q23, Q24		Q32, Q39, Q40
Adherence	Q33, Q35, Q41, Q44, Q45	Q46	Q18, Q19, Q20, Q21, Q22	Q25	Q26, Q29, Q34
Regular monitoring/ HIV-1 seroconversion	Q34		Q14		Q27, Q28, Q31, Q35, Q36, Q37, Q38

Abbreviations: HCP, Healthcare provider; HIV, Human immunodeficiency virus; Q, question.

Assessment of success

For the HCP and CAB-LA user surveys, the proportion of correct or appropriate responses to the access, knowledge, attitude (for HCP), and behaviour questions related to the primary objective will be summarized, across questions, categories (access, knowledge, attitude, behaviours) and participants.

For this study, a success threshold (i.e., optimal knowledge, attitude, and behaviour) of 80%, which is commonly used by convention,[41,40] will be adopted at the individual level. In other words, an individual will be deemed to have met the success threshold if they answer ≥ 80% of questions within each KAB domain correctly or appropriately. Therefore, there will be a separate score for knowledge and behaviour. At the population level, we propose a success cut-off of 70% defined as at least 70% of HCPs and CAB-LA users meeting the success threshold (i.e., answer ≥ 80% of questions within the KAB domain correctly or appropriately) at the time of assessment.

While some published KAB studies have conducted surveys at two time points, we will be conducting a one-time assessment because we anticipate that 70% of HCPs and CAB-LA PrEP users surveyed would likely achieve the success threshold.

Additional justification for conducting a one-time assessment is based on several challenges associated in conducting a two-time point outcome assessments among HCPs and CAB-LA users, which include: 1) evolving PrEP prescribing practices may lead to an expansion in HCPs prescribing PrEP over three years,[42] and this demographic change in the profile of prescribers would make KAB trend comparisons between 18 months and at a future time (e.g. 3 years) less meaningful; 2) competing therapies, public health priority changes, and updated guidelines could shift user preferences or prescribing patterns, impacting CAB-LA uptake and introducing confounding variables that could undermine the ability to assess trends in retention reliably;[42-44] and 3) users may discontinue CAB-LA or switch providers between 18 months and a future time (e.g., three years), posing challenges in maintaining a consistent cohort for meaningful comparisons over extended periods and determining if knowledge is retained, increased, or decreased by users. By concentrating efforts on the 18-month survey, we will obtain valuable insights on the KAB levels among HCPS and CAB-LA for PrEP users within a stable context while avoiding confounding variables and practical challenges associated with a longitudinal two-time point timeline.

Outcome Variables – Secondary objectives

For the secondary objectives, the HCP survey will collect data on HCP decision-making processes, experience prescribing or managing CAB-LA and oral PrEP use among their users, use of CAB-LA oral lead-in and oral bridging, -management of PK tail among those discontinuing CAB-LA, and attitudes towards CAB-LA.

The CAB-LA user survey will collect data on users' decision-making process related to the use of oral PrEP and CAB-LA and reasons for initiating, switching to, or staying on CAB-LA; experiences with CAB-LA, including satisfaction and acceptability of the regimen, PrEP-related preferences, any benefits or limitations of HCP visit schedule, and the emotional and daily life impacts of using CAB-LA, utilization patterns of CAB-LA, and experiences of judgement for using CAB-LA and other PrEP.

The survey questions associated with each objective are presented in Table 8.

Table 8. Survey questions categorization by secondary objective

Objective	User Survey	HCP Survey
Demographics and clinical characteristics	20 questions	13 questions

Objective	User Survey	HCP Survey
Decision-making for PrEP and CAB-LA	3 questions	4 questions
Experience and satisfaction using PrEP and CAB-LA	12 questions	17 questions
CAB-LA oral lead-in and bridging (HCPs)	NA	8 questions
Management of PK tail (HCPs)	NA	5 questions
Attitudes towards CAB-LA (HCPs)	NA	2 questions
Utilization patterns (includes oral lead-in and bridging, and discontinuation; users)	19 questions	NA

Abbreviations: CAB-LA, Long-acting injectable cabotegravir (Apretude®); HCP, Healthcare provider; PK, pharmacokinetic; PrEP, Pre-exposure prophylaxis

HCP survey

The following variables will be extracted from the HCP survey:

Table 9. HCP survey topics categorized by secondary objective

Objective	Survey Topic
Decision making process for use of oral PrEP and CAB-LA	• Who is offered PrEP • Factors influencing decision to offer oral PrEP and CAB-LA • Prescribers' insights into user preferences (prescribers only) • Reason for not initiating CAB-LA
Experience prescribing and managing users on oral PrEP and CAB-LA, at the clinical level and among eligible individuals, including use of HIV testing	• Factors influencing the number of CAB-LA users that clinics can manage • Reasons for switching PrEP methods • Identifying number of patients who could be potential CAB-LA users • Barriers to implementation of CAB-LA • Frequency of HIV and STI testing for patients on oral PrEP and CAB-LA • Type of HIV testing • Clinics' ability to have non-prescribers administer oral PrEP;

Objective	Survey Topic
	• Authorization of who can administer oral PrEP and Apretude • Decision-making process for discontinuing CAB-LA (prescribers only) • Proportion discontinued CAB-LA • Measures taken in the first week on CAB-LA • Reasons for discontinuing CAB-LA
Use of oral lead-in and oral bridging	• Candidates for oral lead-in (prescribers only) • Oral lead-in drug, frequency and duration • Decision-making processes for oral lead-in (prescribers only) • Oral bridging drug, frequency and duration • Decision-making processes for oral bridging (prescribers only) • Oral lead-in and bridging drugs prescribed
Management of pharmacokinetic tail among those who discontinue CAB-LA	• User counseling regarding residual CAB-LA concentrations • Timing of counseling • Monitoring of patients after discontinuation • Patients use of oral PrEP after discontinuing CAB-LA • Duration of oral PreP use after discontinuing CAB-LA, by sex
Attitudes towards CAB-LA	• Opinions regarding administering and implementing CAB-LA • Perceived benefits of implementing CAB-LA in practice

User survey

The following variables will be extracted from the user survey:

Table 10. User survey topics categorized by secondary objective

Objective	Survey Topics
Decision-making processes for use of oral PrEP and CAB-LA	• Level of shared decision-making • Prior treatment • Reasons for initiating CAB-LA
Experience using oral and CAB-LA, including emotional and daily life impact and treatment satisfaction	• Satisfaction with medication • Drug administration preferences • Limitations of CAB-LA • PrEP preferences

Objective	Survey Topics

	• Satisfaction with injections over oral PrEP
	• Worry of missing doses
	• Judgement due to use of oral PrEP prior to CAB-LA
	  ○ Frequency, occurrences, feelings associated
	• Judgement due to use of CAB-LA
	  ○ Frequency, occurrences, feelings associated
	• CAB-LA impact on unfair judgement

Utilization patterns include adherence, oral lead-in, bridging and discontinuation	• Oral lead-in use and reasons for use • Missed injections ○ Planned vs. unplanned, reasons for missing • Use of and type of oral bridging • Acceptability of oral bridging • Current CAB-LA use status • Reasons for continuing CAB-LA • Reasons and decision-making processes for discontinuing CAB-LA • Receipt of counselling for HIV testing after discontinuation • Acceptability of HIV testing after discontinuation • Using other PrEP after discontinuing CAB-LA • Receipt of counselling to initiate another PrEP after discontinuing CAB-LA • Acceptability of counselling to start another PrEP • Future consideration of CAB-LA

Apretude Support PSP

The following variables will be extracted from the PSP database:

Table 11. Variables extracted from the Apretude Supports Program database

Apretude Supports Program database variables
• Patient ID
• Enrolment date
• Patient status
• Patient status date
• Appointment number
• Oral lead-in use

Apretude Supports Program database variables
• Initiation injection dosing schedule
• 2nd initiation injection dosing schedule
• Days supplied
• Injection type
• First dose date
• Initial injection dose
• Current injection dose
• Baseline target treatment date
• Current target treatment date
• Appointment dates o Confirmed appointment, missed appointment, cancelled/rescheduled appointment, patient file appointment
• Reason for missed injection
• Oral bridging use o Planned/unplanned oral bridging, oral bridging agent, dose, planned leave start and end dates
• Returned appointment date or target treatment date
• Re-initiation appointment date
• Status date discontinued
• Status reason discontinued o Missed injection status
• Incomplete reason

The following utilization pattern outcomes will be assessed based on the PSP data:

Table 12. Outcome assessed for secondary objective #9

Category	Sub-category	Details
Utilization patterns	• Use of oral lead-in	▪ Frequency of use ▪ Duration of use
	• Use of oral bridging	
	• Adherence to CAB-LA	▪ Measured as proportion of days covered (PDC) o Ratio of number of days the user is covered by the medication during a specific period to the total number of days within that period • Measured on user's coverage (days supplied) with CAB-LA

Category	Sub-category	Details
		• Based on available follow-up time within the Apretude Supports Program database
	• Timing of injections (relative to labeled dosing schedule)	▪ Early, on-time, late (with 7-day grace period)
	• Gaps in therapy	▪ Missed injections (relative to labeled dosing schedule), reasons for missed injections ▪ Missed injections being planned or unplanned ▪ Use of oral bridging, planned or unplanned o Type and frequency of oral bridging agents used o Duration of oral bridging
	• Persistence on CAB-LA	▪ Time to discontinuation ▪ % of users who remain on drug, and are still at risk of HIV infection, at end of follow-up (will depend on data availability for at-risk status, either through PSP variables or through linkage with survey data)
	• Discontinuation	▪ Rates of discontinuation ▪ Reasons for discontinuation

7.3.3. Confounders and Effect Modifiers

None identified

7.4. Data Sources

Primary Objectives

This study will include data collection through surveying of HCPs and CAB-LA users. The HCP study population will comprise physicians, nurses, and pharmacists who prescribe

CAB-LA or who manage CAB-LA use among CAB-LA users in Canada. HCPs will be recruited across different clinical settings representative of how care is offered in Canada, including but not limited to hospitals, outpatient clinics, and pharmacies across Canada. CAB-LA users will be recruited from different clinical settings where they access PrEP (for example, but not limited to hospitals, outpatient clinics, and pharmacies) across Canada.

Secondary Objectives

For the secondary objectives, this study will include data collection through surveying of HCPs and CAB-LA users and a retrospective analysis of data from the Apretude Supports Program.

Apretude Supports Program Database Analysis

The retrospective database analysis will utilize the Apretude Supports Program database run by a third-party vendor (Bayshore Healthcare), which is responsible for managing and administering the program, including capturing participant information in the Apretude Supports Program database. Enrolment forms for the Apretude Supports Program which are sent to Bayshore Healthcare include participants' informed consent to allow ViiV Healthcare and Bayshore Healthcare to collect, use and analyze Apretude Supports Program data for the purposes of research. The data collected by Bayshore may be collected in aggregate and anonymized form and used for research (per patient consent in the enrollment form). Data will be included for individuals initiating CAB-LA between July 2024 and October 2026, with an interim analysis taking place in Q1/Q2 2026 for data available up to that time point (July 2024 to Q1/Q2 2026). As this will be an analysis of already collected data (secondary data collection), variables and data will be dependent on the data collected with the Apretude Supports Program, as detailed in Annex 1.

7.5. Study Size

7.5.1. Sample Size Calculation

Primary Objectives

HCP and CAB-LA User Survey

As the outcomes for this study are largely descriptive in nature, standard sample size calculations based on hypothesis-testing are not relevant. However, sample sizes can be selected to achieve target levels of precision for resulting confidence intervals around the estimate calculated. Sample size calculations presented here are focused on primary objectives 2 through 4 (KAB survey); primary objective 1 and all secondary objectives based on the survey are purely descriptive and do not reflect key KAB outcomes and as such, are not drivers of sample size decisions. Additional secondary objectives will make use of the Apretude Supports Program and the sample size will be outside of investigator control and determined by the size of the corresponding retrospective database.

The table below provides the precision (expressed as +/-% in upper and lower confidence bounds), based on a normal approximation to the binomial, for a range of sample sizes and response percent values. The response percent values correspond to the percentage of correct responses to the key KAB questions in the HCP and CAB-LA user surveys, for the primary study objectives. Based on the properties of the binomial distribution, variation (and hence sample sizes) is by definition highest if the true correct percentage is 50%,[45] so for a given sample size precision is lowest for an assumed 50% correct response rate. Note that variance is symmetrical such that the precision for a 60% correct response rate would be equivalent for a correct response rate of 100-60=40% correct response rate and so on.

In this sample size calculation, it was assumed that there will be no correlation across respondents (e.g. due to HCPs and multiple users from the same clinical practice). If correlation across users is present, the precision will be increased (i.e., narrower confidence intervals) relative to that indicated below due to a more narrowed sampling strategy which potentially reduces the generalizability of results.

Table 13. Levels of precision calculated by target sample size and proportion of correct responses

	Correct response rate (%)				
Sample size	50	60	70	80	90
50	+/-13.9	+/-13.6	+/-12.7	+/-11.1	+/-8.3
100	+/-9.8	+/-9.6	+/-9.0	+/-7.8	+/-5.9
250	+/-6.2	+/-6.1	+/-5.7	+/-5.0	+/-3.7
500	+/-4.4	+/-4.3	+/-4.0	+/-3.5	+/-2.6

For binary % outcomes, based on the maximum variation assumption (p=0.50), the expected 95% confidence interval precision is +/- 9.8% for a sample size of 100 and +/- 6.2% for a sample size of 250.

The target sample size for the HCP survey is n=100 HCPs; the target sample size for the CAB-LA user survey is n=250. Thus, with respect to the primary study objective as reported by users, the maximum width of the expected confidence interval is +/- 9.8% for HCPs and +/- 6.2% for users.

Secondary Objectives

HCP and CAB-LA User Survey

The HCP and CAB-LA user participants will complete one survey, addressing questions for both the primary and secondary objectives.

Apretude Supports Program Database Analysis

The sample for the Apretude Supports Program database analysis will include eligible CAB-LA users in the database at the time of the interim and final analyses. It is anticipated that at least 450 eligible CAB-LA users will be included at the time of final analysis.

7.5.2. Recruitment strategy

Pilot testing

Pilot testing for the surveys will be conducted as the final stage of survey development (before REB submission) to identify and address potential issues that could affect data quality, including reducing incomplete responses, assessing clarity and understandability of questions, evaluating the appropriateness of language and terminology, estimating the time required to complete the survey, and ensuring that the structure and flow of the survey are logical and user-friendly. Five participants will be sought to pilot test the survey and provide feedback (five HCPs for the HCP survey, and five CAB-LA community members (i.e. AIDS support organization workers who provide support in the care of PrEP users) for the user survey). Each of these participants will participate in a one-on-one virtual session to review the survey with a study team member and provide feedback on the survey questions and response options. Feedback from these sessions will be reviewed by the research team and used to improve and implement any relevant changes to the survey. Once the feedback is compiled, the surveys will be updated as needed and general recruitment will commence as described below. The pilot testing will not collect any data to be analysed or included in the study database.

Recruitment of HCPs

The recruitment strategy will target HCPs across different institutional and community settings representative of how care is offered in Canada, including but not limited to hospitals, outpatient clinics, pharmacies, community clinics, and private practices across Canada. Recruitment will be stratified by provider type. To adequately address objectives related to prescriber decision making, given that not all HCPs administering injections will be the ones making prescribing decisions, a minimum target of 50% prescribers has been set (i.e., recruitment for non-prescribing HCPs will be halted once the sample size reaches 50). HCP recruitment may take place through an established recruitment vendor for medical research (Medicys), with minimum targets for recruitment by prescriber status, clinical setting, and HCP type. Recruitment and survey materials for the secondary objectives will not contain language suggesting that the study was requested by HC.

Table 14. Target sample sizes according to selected characteristics

HCPs (total n = 100)	
Characteristic	**Minimum n**
Prescriber status	
Prescribes or can prescribe CAB-LA	50
Clinical setting	
Hospital	25
Outpatient clinic	25

HCPs (total n = 100)	
Pharmacy	25
HCP type	
Physician	15
Nurse	15
Pharmacist	15

Abbreviations: CAB-LA, Long-acting injectable cabotegravir (Apretude); HCP, Healthcare provider.

Recruitment of CAB-LA Users

For the survey component of the study, CAB-LA users will be recruited using recruitment flyers/posters with a quick response (QR) code linked to the survey, displayed at different clinical settings where they access PrEP (for example, but not limited to hospitals, outpatient clinics, and pharmacies) across Canada. In addition, HCPs participating in the HCP survey may also direct CAB-LA users to the QR code for the survey. To reach target sample sizes and to ensure representativeness of the user sample, recruitment may additionally be conducted through Medicys. Recruitment of CAB-LA users will be conducted in geographic regions where CAB-LA is publicly listed. As access expands across Canada, recruitment will also be expanded to ensure representation from all possible regions. The data will be analyzed by geographical location, with some regions anticipated to be grouped together based on available sample size (e.g., Western Canada). Recruitment and survey materials for the secondary objectives will not contain language suggesting that the study was requested by HC.

Logistics and Monitoring

Individuals who are interested in participating will be directed to a brief screening questionnaire to assess eligibility for survey participation against study inclusion criteria. If the individual is identified as eligible to participate in the survey based on screener responses, they will be directed to an electronic version of the consent form. Once they have electronically indicated their consent to participate (selecting a consent statement and providing an electronic signature), they will subsequently be directed to complete the survey. Based on personal information collected during the screening and consent process, including participant name and email address, a check will be performed to ensure that there is no prior completion of the same survey in the system using the same name and email entered. The purpose of this check is to prevent participants from completing the same survey multiple times. To help optimize response rates, up to two reminder emails will be sent to individuals who have not completed the survey (one after 7 days and another after 14 days). To promote further education, correct responses to the survey questions, where applicable, will be displayed immediately after submission of the survey (before a participant has exited the survey) in a PDF file. A link to the aRMMs will be included in the PDF and on the online survey platform for future reference.

For each survey, a live dashboard will be set up to monitor recruitment progress against targets, allowing for adjustments to the recruitment strategy to be made in real time, as needed (e.g., increase the number of recruitment sites and/or target recruitment of certain participant groups to improve representativeness).

HCPs will receive a one-time payment of $350 upon completing the survey, while CAB-LA users will receive $100. For the pilot testing, each of the 5 HCPs will be compensated $350, and each of the 5 community members will receive $100. Remuneration details will be provided in the consent form. For both surveys, unique survey links will be generated for each participant. The unique link will enable participants to save their progress and return to complete the survey at a later time, minimizing potential incomplete responses. In addition, checks will be in place to ensure that each link can only be used once to complete the survey and receive payment. Checks may include a combination of the following: 1) checking IP addresses; 2) checking for duplicate email addresses for payment; 3) checking for suspicious email addresses; 4) running PercentMatch statistical function assess the level of identical observations in the survey dataset; 5) checking for realistic survey completion times. Recruitment will continue for approximately five months, unless the closing criterion is met. The closing criterion for the survey is reaching the maximum sample size of 100 HCPs and 250 CAB-LA users.

7.6. Data Management

For the primary objectives, this study will include data collection through cross-sectional HCP and user surveys.

For the secondary objectives, this study will include data collection through cross-sectional HCP and CAB-LA user surveys, as well as a retrospective analysis of the Apretude Supports Program.

The HCP and user surveys will be available as a secure custom online survey, that will be compatible with mobile phones and computer platforms. Additionally, the user survey will be available as a paper option for users to complete at participating clinical study sites, as needed.

7.7. Data Analysis

The analysis for the study will primarily be descriptive and will be guided by the statistical analysis plan and shell results tables for the study. To analyze and synthesize study data, in general, binary and categorical outcomes, endpoints will be presented as numbers (N) and percentages (%). Continuous endpoints will be presented using mean, standard deviation (SD), median, interquartile range (IQR), 95% CIs, minimum, and maximum values.

Results will be reported overall and by characteristics of interest (i.e., for HCP survey, by HCP type [e.g. physician, nurse, pharmacist]; for user survey, the location of practice where they receive CAB-LA (institution vs. community]).

All analyses will be performed in R (R Foundation for Statistical Computing, Austria). Additional publicly available packages used may include tidyverse for data cleaning and manipulation, openxlsx for reading and exporting Microsoft Excel files, ggplot2 for creating data visualizations, stringr for manipulating text data, and officer and rvg to print R outputs to Microsoft Word or Microsoft Powerpoint.

To ensure robustness of study findings, a sensitivity analysis will be conducted, if necessary, to exclude data collected from individuals who are deemed to have contributed poor quality responses. Specifically, participants may be flagged for exclusion if they provide inconsistent responses to a question repeated within the survey to test consistency, and/or if their total survey completion time falls below a threshold that suggests insufficient engagement with the survey. The threshold will be determined based on the distribution of completion times in the study sample and in consultation with the GSK team (the estimated total completion time is 30 minutes for the HCP survey [14 minutes for the primary objective questions] and 35 minutes for the user survey [13 minutes for the primary objective questions]). The sensitivity analysis will compare results with and without exclusion of flagged participants to evaluate the potential impact of poor-quality data on the findings of the study.

7.7.1. Primary Analysis

7.7.1.1. Main Analytical Approach

Primary Objectives

The characteristics of HCPs and CAB-LA users will be summarized as frequencies and percentages (categorical variables) or as means, SD, medians and IQR (continuous variables). These will be summarized overall, by characteristics of interest (i.e., for HCP survey, by HCP type [e.g. physician, nurse, pharmacist]; for user survey, whether a user is a naïve or experienced with PrEP use, the location of practice where they receive CAB-LA (institution vs. community]) will be included in the stratified analyses.

The cross-sectional survey questions – addressing HCP and CAB-LA user knowledge, attitudes, and behaviours – will largely have categorical response options and will also be summarized as frequencies and percentages. By design, most survey data collected will be categorical. The proportion of correct and appropriate answers to key survey questions will be summarized, among those HCPs and CAB-LA users who provided responses to those questions (missing data will be summarized but not counted as a denominator in the proportions). The number and percentage of HCPs and CAB-LA users who have provided correct responses to knowledge questions will be summarized for each question, as well as the number and percentage of HCPs and CAB-LA users who have provided correct responses to at least 80% of all questions (target threshold for the study based on previous studies).[41] Similarly, the number and percentage of HCPs and CAB-LA used who have provided responses indicative of optimal behaviour will be summarized for each question. Specific behaviours will be identified where less than 80% (or alternative thresholds) of participants reported optimal behaviour. Results will be presented overall for HCPs and CAB-LA users, as well as stratified by characteristics of interest (see section 7.7.2 for details). Free-text response options will be summarized for specific questions.

In addition to numeric results tables, customized visualizations will be developed to convey survey results for HCPs and CAB-LA users. These will include various histograms or bar charts to display the distribution of HCP and CAB-LA user responses for key survey items.

The participation rate (i.e., the proportion of participants completing the survey among those who consented to participate) for the HCP and CAB-LA user surveys will be assessed, as well as the level of completion of surveys and missing data among those who participated in the survey study. In cases where a significant amount of missing data is observed, we will conduct a comparative analysis between participants who completed the survey and those who did not, to determine if systematic differences exist between these groups. This analysis will help guide our strategy for addressing missing data, which may include sensitivity analyses to minimize potential biases in our findings.

Secondary Objectives

For both the survey and the retrospective cohort analysis, the characteristics of HCPs and CAB-LA users will be summarized as frequencies and percentages (categorical variables) or as means, SD, medians and IQR (continuous variables). These will be summarized overall and by characteristics of interest (see section 7.7.2 for details).

The survey questions will largely have categorical response options, which will be summarized as frequencies and percentages. The analysis will be guided by shell tables developed based on the final version of the survey. Results will be presented overall for HCPs and CAB-LA users, as well as stratified by characteristics of interest (see section 7.7.2 for details). The participation rate for the HCP and CAB-LA user surveys will be assessed, as well as the level of completion of surveys and missing data among those who participated in the survey study.

The retrospective cohort analysis used to understand utilization patterns will be summarized as frequencies and percentages (categorical variables) or medians and IQR (for continuous variables). The analysis will be guided by shell tables developed based on data available through the Apretude Supports Program. Results will be presented overall for CAB-LA users and stratified by characteristics of interest (see section 7.7.2 for details).

In addition to numeric results tables, customized visualizations will be developed to convey survey results for HCPs and CAB-LA users, and retrospective cohort analysis results for CAB-LA users. These will include various histograms or bar charts to display the distribution of HCP and CAB-LA user responses for key survey items and key utilization metrics.

The participation rate for the HCP and CAB-LA user surveys will be assessed, as well as the level of completion of surveys and missing data among those who participated in the survey study.

7.7.2. Secondary Analysis/CCI [redacted]

Analyses will be stratified by key demographic and clinical characteristics of interest (i.e., for HCP survey, by HCP type [e.g. physician, nurse, pharmacist]; for user survey, the location of practice where they receive CAB-LA (institution vs. community]) among users in the PSP database, should this data be available. For the user survey, a stratified analysis by prior oral PrEP use before starting CAB-LA will also be conducted. CCI [redacted]

CCI

[redacted]

CCI

[redacted]

7.8. Quality Control and Quality Assurance

This study will be conducted according to local quality control processes. This procedure requires documented evidence that the study protocol has been correctly interpreted and executed.

This study will be conducted according to published best practices and guidance on the conduct of quantitative surveys, as well as Broadstreet Health Economics and Outcomes Research (HEOR) working practices to guide statistical analysis and validation. Details of these procedures are listed below, as are the details of a quality control (QC) independent review of final results to ensure that the study protocol has been correctly interpreted and executed.

Data will primarily be collected through securely hosted online surveys. CAB-LA users will have the option to complete a paper survey. The online surveys will be designed to not allow questions to be skipped (to avoid incomplete data); however, participants may select a "prefer not to answer" option, in particular for sensitive questions. Thus, incomplete questions are not expected for the online surveys; however, incomplete questions may occur for the paper survey. No imputation is planned for any missing data (incomplete questions or questions marked 'prefer not to answer'). All data collected will be considered for the analysis, including for partially completed surveys. However, measures will be taken to optimize response rates (see section 7.5.2).

Additionally, the surveys will be designed to minimize the possibility of participants entering inappropriate responses. These design elements include using close-ended, true/false or multiple-choice options; allowing users to respond with "I'm not sure" or "Prefer not to answer" rather than participants entering erroneous responses; and restricting free text responses to only accept numeric data entries (where appropriate, e.g., entering participant age).

After the completion of the first surveys by HCPs and CAB-LA users, an analyst will assess response rate, as well as the quality of collected data. Data will be checked for missing, illogical, and inconsistent data, and automated data checks will also be conducted (e.g., range checking). Any implications regarding survey programming will be identified and

implemented in the online surveys. Similar data checks will be re-conducted after survey recruitment has been closed. All modifications to the database will be clearly documented, and the study database will only be accessible to authorized study personnel.

During data analysis, certain data cleaning steps may be implemented. Numeric variables such as participant age will be reviewed for minimum and maximum, to identify any values that are likely to be data entry errors. Variables may be renamed from the raw survey data with shorter and more intuitive names for analysis. The list of variable names will be documented.

All analyses will undergo a QC review by an additional analyst not involved in the conduct of the original analyses. The QC analyst will review all programming code for population creation and results tables generated; will independently re-generate sample tables for each results section; and will verify the accuracy of all numeric values reported.

7.9. Limitations of the Research Methods

This study is subject to several limitations. Firstly, there is the potential for selection bias, given the voluntary nature of participation in the survey study, for both HCPs and CAB-LA users. Additionally, although efforts will be made to recruit a representative sample of different types of HCPs and CAB-LA users from different settings, the sample included in the study may not be representative of all HCPs and CAB-LA users. Further, given the self-reported nature of the data within this study, there are a number of additional biases to consider. First, self-reported data may be subject to reporting bias; second, recall bias may play a role in accurately remembering information, for example for questions related to CAB-LA user behaviours. Furthermore, given that the correct answers to the questions assessing knowledge can be identified by referring to the aRMMs, the consent form and survey instructions will clearly state that the intent of the survey is to assess general levels of knowledge and awareness, and that participants' responses cannot be linked back to them, in order to encourage participants to respond based on their own knowledge without referring to other materials. Lastly, CAB-LA users within the PSP may have important differences from those who are not in the PSP, therefore, the data may not be generalizable to all individuals who would receive CAB-LA. CCI [redacted]

All limitations mentioned in this section will be included in the final study reports.

7.10. Other Aspects

In the event that KAB success thresholds are not reached, it will be important to identify possible reasons for failure and areas for potential intervention and improvement. By design, the survey will include questions that are not used in the scoring of KAB, but used to understand general use of aRMMs and potential reasons for suboptimal use. Free-text

response options will be available in key questions in order to capture rich information that may inform strategies to improve the uptake of the optimal behaviours detailed in the aRMMs.

Since Apretude's approval in Canada in May 2024, the GSK/ViiV medical team has proactively developed programs for HCP education which can be leveraged if appropriate. These programs are based on a national learning needs assessment for HIV prevention and include other faculty-driven learning activities that provide key information on PrEP in general, but also on new modalities like Apretude. The educational focus is on acquiring knowledge (in-depth data review), but also on attitude and skills (data-light with focus on experience sharing and practical tips & tricks) to support HCPs in the safe use of Apretude. Another tool recently made available to HCPs is the Apretude Prevention Guide, which was developed by a group of experts across Canada, including infectious diseases specialists, family physicians, nurse practitioners and pharmacists specializing in HIV and PrEP. Of note, the details of the aRMMs as well as its resource page is provided to HCPs in this guide.

Based on the survey methodology, we expect that we will be able to identify whether the low level of success follows specific trends. For example, suboptimal behaviour in managing users who discontinue the regimen may be associated with a specific type of HCP, low levels of knowledge about adherence among users may be linked to specific regions, or systematic demographic differences may exist between participating groups, such as those with missing data compared to those who completed the survey. If so, we will focus our efforts on leveraging the existing education resources and adapting/tailoring them to appropriately addressing these gaps identified from this study.

It is anticipated that this corrective action plan will address any educational gaps that may be identified from the surveys.

Additionally, pilot testing will be conducted for the survey, to help ensure questions and response options, structure and programming, are best designed to minimize incomplete or inaccurate responses. If needed, the study protocol and survey questions may be re-evaluated and adapted for a re-assessment of KAB outcomes at 3 years.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

This observational study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, Good Participatory Practice (GPP) and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

Ethical approval for the study will be sought from the appropriate REBs for the study, which is anticipated to include both Institutional Review Boards (IRBs) and an

Independent Ethics Committee (IEC), as appropriate for each included clinical site. The REBs must also approve any amendment to the protocol, according to local regulations.

User Survey

Prior to completing the survey, all potential participants will be able to read the informed consent information, either electronically or as a paper version (if they select to complete a paper survey at a participating study site (to be confirmed). Consent will be indicated through the selection of a consent statement, and the provision of the participant's name, signature (electronic or wet ink, as appropriate), and the date of consent.

Apretude Supports Program Analysis (Secondary objectives)

Participants in the Apretude Support PSP will have previously provided informed consent during enrolment and this consent permits the use of the participants' data for further research activities. Thus, no additional consent will be required for the purposes of this study.

8.2. Subject Confidentiality

All participants will be assigned a unique study identification (ID) in the study database, that will not be linked to personal identifiable information. GlaxoSmithKline (GSK) will not have access to patient identifiers.

9. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

The authors confirm that study data is Individual Human Data (IHD) owned by GSK and that:

- The proposed use of the IHD is **Study Use*** as outlined in the patient consent/consent waiver (HCP and User Surveys).
- The study IHD will be anonymized as described in VQD-STD-000324 (Apretude Supports Program Analysis).

* Study Use means - the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the product studied and the disease/condition studied. This includes bringing the product to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

Ex. Protocol Final

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study has safety objectives. Safety collection and reporting will correspond to the following study type:

HCP and CAB-LA User Surveys **Study type 1**: Primary data collection studies with or without sites/investigators with safety objectives (or systematic collection of adverse events) where there is consent and/or data collection direct from patients.	*These studies can identify solicited and spontaneous events*
Retrospective Cohort Analysis **Study type 5:** Secondary data collection studies including unstructured data with human review with safety objectives. An example is human review of verbatim text in a medical record as part of a chart review study.	*These studies can identify pre-specified safety events in aggregate at prespecified study milestones (e.g., interim analysis, study end) study end but cannot identify spontaneous events*

Collection of adverse events/reactions (Solicited Events)

HCP and CAB-LA User Surveys

Solicited Events are defined as adverse events related to the GSK/ViiV product under evaluation, identified and systematic collected in the study database.

The primary objectives of this study are to evaluate the effectiveness of the aRMMs for CAB-LA within Canada. For the primary objective, the study outcomes will be collected using closed ended questions only and are related to the aRMM effectiveness endpoints that will not be collected and reported as safety events.

The secondary objectives of the study include describing the users' experience of CAB-LA, the utilization patterns, including adherence and persistence, and reasons for discontinuation, which may include adverse events. Certain responses to specific questions in the User survey, as defined in the Safety Management Plan, will be captured as solicited events and systematically collected and entered in the study database during the study. These events should be reported to the GSK Safety department (timing and contact information provided in the safety management plan). Solicited events must be collected in the study database and reported to GSK for entry into the GSK Safety database. For primary data collection studies, where there is direct collection of data from patients, these will be classified as solicited individual

case safety reports (ICSRs). Valid ICSRs will be managed, classified, and submitted for onward reporting to regulators in line with the appropriate time frames as detailed in the Safety Management Plan.

These will also be summarised in interim, if applicable, and final study reports.

Adverse events related to CAB-LA that are not systematically collected will be reported as spontaneous events as described below (see reporting section below).

Due to the well characterised safety profile of CAB-LA under evaluation; only the safety events specified in the study objectives will be solicited and systematically collected during the study.

Retrospective Cohort Analysis

For CAB-LA exposed patients, pre-defined safety events of interest (e.g, reasons for discontinuation, which may include adverse events), will be systematically recorded in aggregate. These will be summarised in final study reports. This analysis is based on secondary use of existing health data and as such Individual Case Safety Reporting (ICSRs) to regulatory agencies is not required. These events are not entered into the GSK Safety database but review of study reports from the QC'ed study database will be performed by Global Safety as appropriate.

Reporting of adverse events/reactions (Spontaneous Events)

HCP and CAB-LA User Surveys

Spontaneous Events are defined as:

- Those unsolicited adverse events observed related to the GSK/ViiV product under evaluation but exempted from collection, as justified in the protocol.
- Those adverse events observed related to any GSK/ViiV product not under evaluation in the study.
- Any Adverse Drug Reactions observed related to non-GSK/ViiV product(s), for which the ADRs should be reported to the appropriate marketing authorization application of the product(s) or Health Authority per local regulations. Spontaneous events may be collected in the study database. If events are not collected in the study database, they are still reported to GSK for entry in the GSK Safety database.

Adverse reactions related to the GSK/ViiV product under evaluation, which are not systematically collected/solicited under the study objectives or related to any other GSK/ViiV product will be classified as spontaneous reports and reported to the GSK Safety Department. This includes serious adverse events (SAEs), pregnancies, pregnancy outcomes and incidents (including device deficiencies or malfunctions if applicable).

Healthcare professionals and consumers will be informed of the possibility to report suspected adverse reactions to the marketing authorisation holder or to the concerned competent authority via the national spontaneous reporting system. Study staff will be trained on how to report suspected adverse reactions.

Valid ICSRs will be managed, classified, and submitted for onward reporting to regulators as spontaneous in line with the appropriate time frames.

Spontaneous reports may be linked to specific studies in the GSK Safety database. In the case where they are linked to the study, these reports can also be summarised in interim, if applicable, and final study reports.

ADRs will be reported as spontaneous cases. A Safety Management Plan (SMP) will be developed as per VQD-WI-053775: Non-Interventional Study Safety Management Planning. Reporting timelines and safety contact details will also be provided in accompanying SMP.

Retrospective Cohort Analysis

This analysis is based on data previously collected for other purposes e.g., routine healthcare encounters. As such, there is no requirement for the collection and reporting of Individual Case Safety Reports (ICSRs). Although the study is based on human review of unstructured data, the nature of the secondary data protocol driven data collection and analysis does not allow for reporting of serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK/ViiV product during the conduct of this research. In addition, the minimum criteria of identifiable patient, reporter, exposure and event, needed to report individual case safety reports may not be present in the information reviewed within the context of the study. The data also may lack an identifiable patient and reporter and may be insufficient to establish attribution between a potential safety event and an individual patient using a GSK/ViiV product.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Final results from the primary objectives of this study will be prepared and shared with HC in May 2026. An interim analysis report with results from the secondary objectives of this study will also be prepared for internal dissemination between Q1/Q2 2026 and summarized in an abstract for submission to a scientific conference (to be determined).

A final study report and slide deck will be prepared for internal dissemination of full study findings in November 2027. It is anticipated that an abstract will be prepared for submission to a scientific conference (to be determined). In addition, a manuscript will be prepared for submission to a peer-reviewed scientific journal.

Abstract timing in both instances will depend on conference abstract submission timelines. Manuscript preparation is anticipated to begin in quarter four (Q4) 2027.

12. REFERENCES

1. Organization WH. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022 - 2030. 2022.
2. Tan DHS, Hull MW, Yoong D, et al. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. *CMAJ.* 2017;189(47):E1448-E1458.
3. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. *CMAJ.* 2018;190(25):E782.
4. CATIE. Pre-exposure prophylaxis - Fact sheet. *CATIE FACT SHEET: Pre-exposure prophylaxis* 2023; chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.catie.ca/sites/default/files/2023-06/fs-prep-06152023-en.pdf.
5. Saberi PS, H. On-Demand Oral Pre-exposure Prophylaxis with Tenofovir/Emtricitabine: What Every Clinician Needs to Know. *Journal of Gernal Internal Medicine.* 2020;35:1285-1288.
6. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *The New England journal of medicine.* 2012;367(5):399-410.
7. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England).* 2013;381(9883):2083-2090.
8. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *The Lancet Infectious diseases.* 2014;14(9):820-829.
9. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine.* 2015;372(6):509-518.
10. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *The New England journal of medicine.* 2010;363(27):2587-2599.
11. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *The New England journal of medicine.* 2012;367(5):423-434.
12. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS (London, England).* 2016;30(12):1973-1983.
13. Jourdain H, de Gage SB, Desplas D, Dray-Spira R. Real-world effectiveness of pre-exposure prophylaxis in men at high risk of HIV infection in France: a nested case-control study. *The Lancet Public Health.* 2022;7(6):e529-e536.
14. Canada Go. Government of Canada's sexually transmitted and blood-borne infections action plan 2024 - 2030. 2024; https://www.canada.ca/en/public-health/services/publications/diseases-conditions/sexually-transmitted-blood-borne-infections-action-plan-2024-2030.html.

15. Canada PHAo. Canada's progress towards ending the HIV epidemic. 2023; https://www.canada.ca/en/public-health/services/publications/diseases-conditions/canada-progress-towards-ending-hiv-epidemic.html.
16. Popovic N, Yang Q, Archibald C. Trends in HIV pre-exposure prophylaxis use in eight Canadian provinces, 2014-2018. *Canada communicable disease report = Releve des maladies transmissibles au Canada.* 2021;47(56):251-258.
17. Canada PHAo. Trends in HIV Pre-Exposure Prophylaxis [HIV-PrEP] use in nine Canadian provinces, 2019 - 2022. 2023; chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/trends-pre-exposure-prophylaxis-use-in-9-canadian-provinces-2019-2022-infographic/trends-pre-exposure-prophylaxis-use-in-9-canadian-provinces-2019-2022-infographic.pdf.
18. Tan DHS, Dashwood TM, Wilton J, Kroch A, Gomes T, Martins D. Trends in HIV pre-exposure prophylaxis uptake in Ontario, Canada, and impact of policy changes: a population-based analysis of projected pharmacy data (2015–2018). *Canadian Journal of Public Health.* 2021;112(1):89-96.
19. Tan D, Wilton, J., Allen, V., Burchell, A., Bogoch, I., & Mishra, S. . Estimating the number of gay, bisexual and other men who have sex with men eligible for HIV pre-exposure prophylaxis in Ontario. Paper presented at: Presented at the 26th Canadian Conference on HIV/AIDS Research. 2017b; Montreal, Quebec, Canada.
20. Grace D, Jollimore J, MacPherson P, Strang MJP, Tan DHS. The Pre-Exposure Prophylaxis-Stigma Paradox: Learning from Canada's First Wave of PrEP Users. *AIDS patient care and STDs.* 2018;32(1):24-30.
21. Pico-Espinosa OJ, Hull M, MacPherson P, et al. PrEP-related stigma and PrEP use among gay, bisexual and other men who have sex with men in Ontario and British Columbia, Canada. *AIDS Research and Therapy.* 2022;19(1):49.
22. CATIE. Updated Canadian Guidelines on HIV Pre-exposure Prophylaxis and Post Exposure Prophylaxis. 2024; https://www.catie.ca/survey-provide-feedback-on-canadas-draft-hiv-prep-and-pep-guideline.
23. Marzinke M, Grinsztejn B, Fogel J, et al. Laboratory Analysis of HIV Infections in HPTN 083: Injectable CAB for PrEP. Conference on Retroviruses and Opportunistic Infections; March 6-11, 2021.
24. Delany-Moretlwe S, Hughes JP, Bock P, et al. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women. Paper presented at: HIV Research for Prevention Virtual Conference (HIVR4P 2021).
25. Clinical Trials.gov - Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who Have Sex with Men. Accessed at https://clinicaltrials.gov/ct2/show/NCT02720094. Accessed November 2024.
26. Clinical Trials.gov - Evaluating the Safety and Efficacy of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women. Accessed at https://clinicaltrials.gov/ct2/show/NCT03164564. Accessed November 2024.

27. Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of Human Immunodeficiency Virus (HIV) Infection in Cisgender Men and Transgender Women Who Have Sex With Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083. *The Journal of infectious diseases.* 2021;224(9):1581-1592.
28. Eshleman SH, Fogel JM, Piwowar-Manning E, et al. Characterization of Human Immunodeficiency Virus (HIV) Infections in Women Who Received Injectable Cabotegravir or Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Prevention: HPTN 084. *The Journal of infectious diseases.* 2022;225(10):1741-1749.
29. Product Monograph Including Patient Medication Information for Apretude. ViiV Healthcare ULC. 2024; https://viivexchange.com/content/dam/cf-viiv/viivexchange/en_CA/open/pdf/apretude-pm-en.pdf.
30. Apretude. Apretude Resources (English). https://apretude.ca/en-ca/resources/.
31. Apretude. Apretude ressources (French). https://apretude.ca/fr-ca/ressources/.
32. AM M. Cabotegravir Long-Acting for PrEP Real World Data on On-Time Dosing, HIV Testing and HIV Acquisition from the OPERA Cohort. ID Week 2024 Oral presentation 508; 2024.
33. Miller AC, Arakkal AT, Sewell DK, Segre AM, Tholany J, Polgreen PM. Comparison of Different Antibiotics and the Risk for Community-Associated Clostridioides difficile Infection: A Case-Control Study. *Open forum infectious diseases.* 2023;10(8):ofad413.
34. M R. Real-world use of cabotegravir long-acting for pre-exposure prophylaxis: data from Trio Health cohort. IDWeek; Oct. 16-19, 2024, 2024; Los Angeles.
35. Heise. Key HIV Studies Influencing My Practice Following HIVR4P 2024. HIVR4P Oral presentation OA0503; 2024.
36. Patel. Feasibility of Long-Acting Injectable Cabotegravir PrEP Initiation and Administration by Community Health Workers and Early Aspects of the PrEP Injection Care Continuum in a Primary Care Center in Washington, D.C. IAS 2023, the 12th IAS Conference on HIV Science; 2023.
37. Baker. OA0804LB Early implementation of long-acting injectable cabotegravir for HIV prevention in a safety net primary care centre in U.S. South. HIVR4P
38. Fisher CB, Arbeit MR, Dumont MS, Macapagal K, Mustanski B. Self-Consent for HIV Prevention Research Involving Sexual and Gender Minority Youth: Reducing Barriers Through Evidence-Based Ethics. *J Empir Res Hum Res Ethics.* 2016;11(1):3-14.
39. Flicker S, Guta A. Ethical approaches to adolescent participation in sexual health research. *J Adolesc Health.* 2008;42(1):3-10.
40. Shah SK, Essack Z, Byron K, et al. Adolescent Barriers to HIV Prevention Research: Are Parental Consent Requirements the Biggest Obstacle? *J Adolesc Health.* 2020;67(4):495-501.
41. Sanofi. *Surveys among Health Care Professionals and Patients to assess their knowledge and behaviour with respect to the new (2018) Risk Minimization Measures for valproate use in Europe.* 2020.
42. Canadian Guideline on HIV Pre-Exposure Prophylaxis and Nonoccupational Postexposure Prophylaxis. https://www.catie.ca/canadian-guideline-on-hiv-pre-

exposure-prophylaxis-and-nonoccupational-postexposure-prophylaxis. Accessed February 5th 2025.

43. Government of Canada. HIV in Canada: 2023 surveillance highlights. 2023; https://www.canada.ca/en/public-health/services/publications/diseases-conditions/hiv-2023-surveillance-highlights-infographic.html. Accessed February 5th, 2025.
44. Jefferys R. PrEP and Microbicides Pipeline 2024. 2024; https://www.treatmentactiongroup.org/wp-content/uploads/2024/07/pipeline_PrEP_2024_final.pdf. Accessed February 5th, 2025.
45. Freedman D, Robert Pisani, and Roger Purves. . *Statistics, 4th ed.* 4th, Fourth, 4e ed: W. W. Norton & Company; 2007.

Ex. Protocol Final

ANNEX 1 TABLES

Variable	Description
Patient ID	Anonymized unique program identification number
Enrolment Date	The date on which the patient was successfully enrolled in the PSP
Patient Status	Current status of patient (On drug, Suspended, Discharged)
Patient Status Date	The date the patient was moved into current status
Appointment Number	Sequential appointment number associated with the appointment
Initiation injection Dosing Schedule	Identifies whether the patient is receiving dosing schedule.
2nd initiation injection Dosing Schedule	Identifies whether the patient is receiving dosing schedule.
Patient File Appointments	The date on which drug was dispensed and/or administered
Days Supplied	Days of supply for each dispense/administration
Oral Lead-in	Indicator if the patient initiated the optional a lead-in (i.e., flag and/or date)
Injection type	Description of the type of injection (initiation, subsequent, or re-initiation)
First Dose Date	The date on which the patient initiated their 1st dose of APRETUDE injection
Initial Injection Dose	Dosage as indicated in the initial physician order
Current Injection Dose	Dosage as indicated in the most recent physician order
Baseline Target Treatment Date	Most recently set target date. Modification could be due to planned/ unplanned missed infusions
Current Target Treatment Date	Target treatment date for that appointment record
Confirmed Appointment Date	The date of appointment
Missed Appointment date	Date of missed appointment(s)
Cancelled/Rescheduled Appointment Date	Date of cancelled/rescheduled appointment(s)
Reason for Missed Injection	Reason provided for cancellation/rescheduling of appointment(s)
Planned/Unplanned Oral bridging	Was the cancellation planned or unplanned
Oral Bridging Agent	The type of oral bridging agent taken from the planned missed injection
Oral Bridging Dose	The dosage of oral bridging agent taken from the planned missed injection
Oral Bridging or Planned Leave Start Date	The date on which the patient initiated cabotegravir tablets or other oral PrEP due to a planned missed injection
Oral Bridging or Planned Leave End Date	The date on which the patient discontinued cabotegravir tablets or other oral PrEP due to planned missed injection
Returned Appointment Date or Target Treatment Date	The target date of administration of APRETUDE following a planned missed injection
Re-initiation appointment date	The date of next scheduled appointment after the missed injection/appointment
Status Date Discontinued	The date on which the patient was identified as discontinued or opted out of the APRETUDE SUPPORTS PROGRAM.
Status Reason Discontinued	Reason the patient stopped APRETUDE therapy or left the APRETUDE SUPPORTS PROGRAM.
Missed Injection Status	Description of the patient's status following missed injection (HCP contacted, Oral bridging initiated, oral bridging completed)
Incomplete Reason	Reason the patient did not receive injection. Accompanies an 'incomplete' Injection Status only

Ex. Protocol Final

ANNEX 2 DATA COLLECTION TOOLS

HCP Survey

GK_240144 HIV Apretude_Combined s

User Survey

GK_240144 HIV Apretude_Combined sUser