Information Type: ViiV Healthcare Interventional Study Protocol

Title:	A phase 4, randomized, open-label, three-arm study to evaluate implementation strategies for the delivery of CAB for HIV Pre-exposure Prophylaxis (PrEP) across clinical settings for adult (≥18 years) Black cis-and transgender women without HIV infection living in the United States Ending the Epidemic (EHE) territories
Protocol Number:	217711 (Version 2.0)
Compound Number:	GSK1265744, Cabotegravir
Brief Title:	A study evaluating implementation strategies for the delivery of APRETUDE for Black cis-and transgender women in United States EHE territories.
Development Phase:	Phase 4
Acronym:	EBONI- **E**ngaging **B**lack Women on APRETUDE by **O**ptimizing **N**ovel **I**mplementation Strategies

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Approval Date: 07 Apr 2022

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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 clinical 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 receives the appropriate information throughout the study.

Investigator Name:

_____

_____ _____

Investigator Signature Date

PROTOCOL SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Protocol - Version 2.0	*07 Apr 2022*	*TMF-14337713*
Original Protocol - Version 1.0	*12-JAN-2022*	*TMF-14337713*

Overall Rationale for the protocol update: Information was updated to reflect the safety guidance in the FDA approved APRETUDE USPI Dec 2021 and to provide additional clarification in selected sections.

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LIST OF ABBREVIATIONS

AE	Averse event
ART	Antiretroviral therapy
CAB	Cabotegravir
CBO	Community-based organization
CDC	Centers for Disease Control and Prevention
CFIR	Consolidated framework for implementation research
COVID-19	Coronavirus Disease of 2019
ECI	Enhanced Collaborative Implementation
CI	Confidence interval
DDI	Drug-drug interaction
dsmb	Data and Safety Monitoring Board
DTI	Direct to injection
eCRF	Electronic case report form
EDC	Electronic data capture
EI	Enhanced Implementation
EHE	Ending the Epidemic
FDA	Food and Drug Administration
FIM	Fidelity Intervention Measure
FTC	Emtricitabine
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
IAM	Intervention Appropriateness Measure
ICF	Informed consent form
ID	Identifier
IM	Intramuscular
IMC	Implementation monitoring calls
IRB	Institutional review board
ISQ	Implementation science questionnaire
IS	Implementation science
LA	Long acting
MSM	Men who have sex with men
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OLI	Oral lead-in
PrEP	Pre-exposure prophylaxis
PSP	Patient study participant
SI	Standard implementation
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of Activities
SRM	Study reference manual
SSI	Semi-structured interview

SSP	Study staff participant
STI	Sexually transmitted infections
TDF	Tenofovir disoproxil fumarate
TGW	Transgender women
U.S.	United States
USPI	United States Prescribing Information
VHC	ViiV Healthcare
WOCBP	Women of childbearing potential

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1. ABSTRACT

Background/Rationale: Oral Cabotegravir (CAB) tablets and CAB long acting (LA) extended-release suspension for injection for pre-exposure prophylaxis (PrEP) have been developed to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals (adults and adolescents) weighing at least 35 kg, hereafter referred to as CAB PrEP. The blinded portion of both pivotal studies, HPTN 083 and HPTN 084, were stopped based on Data and Safety Monitoring Board (DSMB) review of available interim data. HPTN 083 demonstrated the superior efficacy of CAB LA when compared to daily, oral tenofovir disoproxil fumarate (TDF)/ emtricitabine (FTC) in men who have sex with men (MSM) and TGW and HPTN 084 demonstrated the superior efficacy of CAB LA when compared to daily, oral TDF/FTC in cisgender women (HPTN 2020a; Landovitz 2021).

CAB LA for PrEP **(hereafter referred to as APRETUDE)** will provide people who vulnerable to HIV acquisition with a new prevention option. It also has several appealing features that could contribute to reducing disparities in HIV infections and PrEP utilization, including superiority vs a daily oral PrEP regimen (TDF/FTC), less frequent dosing and being more discreet; the latter may decrease stigma associated with daily dosing and a pill bottle. However, these features will not overcome the critical existing and new health delivery implementation challenges that must be rapidly addressed when introducing the first injectable HIV prevention option into real-world settings for populations vulnerable to HIV and their providers.

CAB PrEP will provide people who are vulnerable to HIV acquisition with a new prevention option and could contribute to reducing disparities in HIV infections and PrEP utilization. Of the approximately 37K new cases of HIV infection in the United States (U.S.), 19% were among cisgender women and 1% were among transgender women. Among all cisgender women, 55% of diagnoses were among African American/Black women. Among all transgender women, 46% of diagnoses were among African American/Black TGW (Centers for Disease Control and Prevention, 2021; Centers for Disease Control and Prevention, 2019). The Southern U.S. accounted for the highest number of diagnoses of HIV infection among women, with the largest being among African American/Black (22%) women.

Implementation of APRETUDE will require layering on or expanding this new modality to existing PrEP models of care (e.g., clinics and health centers) as well as expanding an injectable delivery to alternative models of care that are already used for oral PrEP (e.g., primary care, telemedicine-supported PrEP delivery and community-based organization delivered PrEP) (Pilgrim, In press). In this study, an innovative set of implementation strategies will be used to address anticipated challenges associated with the appropriateness of APRETUDE delivery in cis- and trans Black women in the U.S. EHE territories that are primarily comprised of states in the Southern U.S.

Objectives:

The primary objective is to evaluate the appropriateness of APRETUDE as assessed by Study Staff Participants (SPPs), comparing the Enhanced Implementation (EI) and to the Standard Implementation (SI) and the Enhanced Collaborative Implementation (ECI) compared to the SI arm over 12 months.

The secondary objectives include the following:

- To evaluate perception of the appropriateness of APRETUDE for patient study participants (PSPs) across study arms at designated time points
- To evaluate adoption of APRETUDE across clinical settings
- To evaluate fidelity to injection and dosing window across traditional and non-traditional settings.
- To evaluate perceptions of barriers, and facilitators to implementation by clinical staff and patients
- To evaluate process of acquiring APRETUDE

Study Design:

This post-approval, Phase 4 study is designed to evaluate the effectiveness of three implementation conditions - Standard Implementation (SI), Enhanced Implementation (EI), and Enhanced Collaborative Implementation (ECI) - on the appropriateness of CAB long acting (LA) for PrEP implementation across clinical settings providing healthcare services to Black cis- and transgender women (TGW) in the EHE territories in the United States (U.S.).

Approximately 21 clinical sites located in EHE jurisdictions will be randomized 1:1:1 in the three implementation conditions. Randomization will occur at the level of study sites and the study team will enroll staff at the study site (who will be enrolled as Study Staff Participants (SSPs)). The PrEP clinics should serve 50% or greater Black patients and/or women, alternatively the site should have greater than 200 adult Black women receiving care at the clinic. These PrEP clinics may vary in scope, such as size and type (e.g., large hospital, small clinic, community clinic, focus on trans individuals, women's health or general primary care). Approximately 250 HIV negative individuals will be enrolled once APRETUDE is prescribed to them; a minimum of 20% and no more than 30% will be transwomen. Patient Study Participants will start APRETUDE using commercial product as prescribed by the PrEP provider. The study will not use a central laboratory, and all laboratory assessments will be performed according to the CDC clinical management guidelines for PrEP and CAB United States Prescribing Information (USPI) using site's local laboratories.

Sites randomized to SI will have access to the standard CAB PrEP toolkits for providers and patients to use as needed along with implementation monitoring.

Sites randomized to the EI arm and the ECI arm will both receive enhanced toolkits for providers and patients and provider education. The EI arm will include a PrEP Options Communication Tool and the ECI arm will include Patient Assessment and Readiness Tools .

Implementation science methodology using both quantitative and qualitative measures will be used to assess the outcomes, to determine effective implementation strategies and to identify barriers and facilitators (including solutions). The implementation outcomes will be assessed from the perspectives of SSPs and PSPs. Clinical data will be collected from PSPs to monitor safety and efficacy.

Analysis Methods:

The primary endpoint in terms of appropriateness is the SSPs mean Intervention Appropriateness Measure (IAM) score at Month 13 under the SI, EI, ECI arms, respectively, and the difference of the SSPs mean IAM scores across the three arms at Month 13.

Descriptive statistics including 95% confidence intervals for these estimates will be displayed. A hypothesis test will be conducted to determine if the observed difference is statistically significant. To address the potential intra-cluster correlation effect due to the cluster randomization design, classical methods such as mixed effects linear regression model or Generalized Estimating Equations will be utilized. Besides the analysis on the participant level, the stratification analysis will be performed at the site level to evaluate the differences in types of sites (primary care vs. women's health, etc.) in responding to the implementation strategies imposed on SSPs. Exploratory analysis will be undertaken to assess the variability of responses by other factors such as subset of implementation strategies. In addition to summary of IAM scores of SSPs at different timepoints, the change in IAM scores of each item from baseline will be analyzed at the designated timepoints.

The IAM scores of PSPs will be summarized in the same way as those of SSPs. In addition, subgroup analysis on PSPs will include factors such as demographic, baseline characteristics and initiation method. To address the potential differential dropout rates of PSPs between arms, appropriate imputation methods will be undertaken to handle missing data of different type.

The analysis methods for the secondary endpoints of acceptability, feasibility, adoption, fidelity of APRETUDE and any adaptations to implementation strategies will be like that of the appropriateness endpoints. CCI [redacted] CCI [redacted]

2. BACKGROUND AND RATIONALE

2.1. Background

CAB (CAB, GSK1265744) is an HIV-1 integrase strand transfer inhibitor (INSTI). CAB, as one component of a dual antiretroviral maintenance therapy regimen in combination with the LA formulation of rilpivirine (RPV LA-Janssen), has been approved in Australia, Canada, the European Union, and the United States for the treatment of HIV-1 infection in adults. Hereafter, CAB + RPV will be referred to as CAB Treatment.

ViiV Healthcare has developed oral CAB tablets and CAB LA extended-release suspension for injection for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in individuals (adults and adolescents) at higher risk of HIV acquisition weighing at least 35 kg, hereafter referred to as CAB PrEP. As a component of the CAB PrEP regimen, CAB tablets (hereafter referred to as CAB tablets for PrEP) may be used as optional oral lead in (OLI) to assess tolerability of CAB prior to administration of CAB LA (hereafter referred to as APRETUDE) and as oral PrEP in individuals who will miss planned dosing with APRETUDE injection.

Two pivotal studies, HPTN 083 and HPTN 084, conducted by the HIV Prevention Trials Network (HPTN) under Sponsorship of the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID)/ National Institutes of Health (NIH). These studies are intended to assess the safety and efficacy of CAB PrEP when compared to the active comparator daily, oral tenofovir disoproxil fumarate (TDF)/ emtricitabine (FTC) for HIV PrEP in the most key affected populations globally (i.e., men who have sex with men (MSM) and transgender women (TGW) [enrolled in HPTN 083] and cisgender women [enrolled in HPTN 084]).

The blinded portions of both pivotal studies were stopped based on Data and Safety Monitoring Board (DSMB) review of available interim data. On 14 May 2020 at a pre-planned interim review of trial data, the DSMB recommended that the blinded phase of HPTN 083 be stopped due to the demonstration of efficacy of CAB LA when compared to daily, oral TDF/FTC (HR 0.34, two-sided superiority $p = 0.0005$) in MSM and TGW and that participants randomized to the active TDF/FTC group be offered CAB LA (HPTN, 2020a; Landovitz, 2021). On 05 November 2020 at a pre-specified interim analysis, the DSMB recommended that the blinded phase of HPTN 084 be stopped due to the demonstration of superior efficacy of CAB LA when compared to daily, oral TDF/FTC (HR 0.11, two-sided superiority $p = 0.000042$) in cisgender women and that participants randomized to the active TDF/FTC group be offered CAB LA (HPTN, 2020b). On May 4, 2021, a New Drug Application was submitted to the US Food and Drug Administration (FDA) for CAB PrEP in the United States (ViiV Healthcare, 2021).

CAB PrEP will provide people who are at high risk of HIV acquisition with a new prevention option and could contribute to reducing disparities in HIV infections and PrEP utilization. Of the approximately 37K new cases of HIV infection in the US, 19% were among cisgender women and 1% were among transgender women. Among all cisgender women, 55% of diagnoses were among African American/Black women. Among all transgender women, 46% of diagnoses were among African American/Black TGW (Centers for Disease Control and Prevention, 2021; Centers for Disease Control and Prevention, 2019). The Southern U.S. accounted for the highest number of diagnoses of HIV infection among women, with the largest being among African American/Black (22%) women. Among transgender women, 43% of diagnoses of HIV infection was in the South. In terms of PrEP, PrEP knowledge and use has been demonstrated to be lower among transgender people and Black cisgender women (Sevelius, 2020; Ojikut, 2018). The Southern U.S. represented only 30 percent of all PrEP users despite accounting for more than half of new HIV diagnoses in the country (Sullivan, 2018).

The existing PrEP disparities are driven by several factors that affect effective implementation, including geography, stigma, medical mistrust, low perception of risk, low awareness of PrEP, lower prescribing behaviors in certain geographies, low healthcare system capacity and low health literacy (Trost, 2020; Jones, 2021; Sullivan, 2018; Ojikut, 2018). APRETUDE has several appealing features that might overcome some of these challenges, including superiority vs oral PrEP, less frequent dosing and is more discreet; the latter may decrease stigma associated with daily dosing and a pill bottle. However, these features will not overcome the critical existing and new health delivery implementation challenges that must be rapidly addressed when introducing the first injectable HIV prevention option into real-world settings for populations vulnerable to HIV and their providers.

Implementation of APRETUDE will require layering onto existing PrEP models of care (e.g., clinics and health centers) and expanding to alternative models of care (e.g., pharmacy-based PrEP, telemedicine-supported delivery of PrEP and community-based organization delivered PrEP) in order to reach populations vulnerable to HIV, especially in the Southern US (Sullivan, 2018; Pilgrim, 2021). Community-based organizations (CBOs) have been critical to the delivery of HIV prevention methods, especially when provided with the right implementation supports, because of their reach and trusted relationship with populations who are vulnerable to HIV, including transgender women (Smith, 2016). Clinical CBOs are more prepared to support expansion of biomedical interventions than nonclinical CBOs (Smith, 2016). According to Black cisgender women, providers with whom they have established a trusting relationship are the best sources of information about PrEP (Auerbach, 2015). The COVID-19 pandemic has significantly expanded the use of alternative models of care. For example, in response to the COVID-19 pandemic, many clinical practices shifted non-essential in-person medical appointments online to reduce the spread of the virus and the rollout of the COVID-19 vaccines has benefited from pharmacy

delivery. These alternative models of care are being used for oral PrEP delivery (Hoth, 2019) and can likely be adopted to support the administration of APRETUDE.

As APRETUDE is introduced to consumers for PrEP, early development, and implementation of strategies to address challenges associated with fidelity and feasibility of its delivery will be important to removing barriers to uptake and persistence by vulnerable populations.

2.2. Rationale

This post-approval, Phase 4 study is designed to evaluate the effectiveness of three implementation conditions - Standard Implementation (SI), Enhanced Implementation (EI), and Enhanced Collaborative Implementation (ECI)- on the appropriateness of APRETUDE implementation across clinical settings providing healthcare services to Black cis-and transgender women (TGW) in the EHE territories in the United States (U.S.).

The study will examine the impact of the SI, EI, ECI on the delivery of CAB PrEP in clinical sites serving Black cisgender women and TGW. As a result, the study will identify strategies that are or are not successful in the delivery of CAB PrEP for Black cisgender women and TGW.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of CAB PrEP may be found in the USPI.

2.3.1. Overall Benefit: Risk Conclusion

The results of this study are anticipated to be beneficial or useful for individuals receiving APRETUDE and physicians providing APRETUDE to provide information about clinical strategies associated with optimal APRETUDE uptake, provision and persistence.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the appropriateness of APRETUDE as assessed by SSPs, comparing the Enhanced Implementation (EI) to the Standard Implementation (SI) arm and the Enhanced Collaborative Implementation arm (ECI) compared to the SI arm	• SSPs mean Intervention Appropriateness Measure (IAM) score at M12(DTI)/M13(OLI)
Secondary	
• To evaluate the appropriateness of APRETUDE by PSPs in the EI compared to SI and the ECI compared to the SI	• SSPs mean IAM score at BL, M4(DTI)/M5(OLI), and M12 (DTI)/M13(OLI) • Change from baseline in SSPs' IAM score at BL, M4(DTI)/M5(OLI), and M12 (DTI)/M13(OLI) • Summary of appropriateness related questions for SSP questionaries as BL, M4(DTI)/M5(OLI), and M12 (DTI)/M13(OLI) • Summary of SSI findings from SSP at, M4(DTI)/M5(OLI), and M12 (DTI)/M13(OLI)
• To evaluate PSPs perception of the appropriateness of APRETUDE in participants enrolled in EI compared to SI and ECI compared to SI over time	• PSPs mean IAM score at BL, M4(DTI)/M5(OLI), and M12(DTI)/M13(OLI) • Change from baseline in PSPs' IAM score at BL, M4(DTI)/M5(OLI), and M12 (DTI)/M13(OLI) • Summary of appropriateness related questions for SSP questionaries as BL, M4(DTI)/M5(OLI), and M12 (DTI)/M13(OLI) • Summary of SSI findings from PSP at BL and M12(DTI)/M13(OLI).

Objectives	Endpoints
• To evaluate adoption of APRETUDE across clinical settings.	• Number of cis-and trans Black women in the clinic who complete a sexual health assessment through M13 in ECI Arm based on site-level PrEP Information Questionnaire • Number of PSPs who complete a sexual health assessment through M13 in ECI Arm based on Site-level PrEP Information Questionnaire • Number and proportion of cis-and trans Black women in the clinic who initiate APRETUDE through M13 by study arm and clinic characteristics based on Site level PrEP Information Questionnaire • Number of cis-and trans Black women in the clinic who continue APRETUDE beyond a first dose through M13 by study arm and clinic characteristics based on Site-level PrEP Information Questionnaire
• To evaluate feasibility and utility of EI tools and strategies compared to SI and ECI compared to SI for APRETUDE	• Absolute values and change from baseline in SSPs mean Feasibility of Intervention Measure (FIM) score for implementation strategies over time • Summary of strategy feasibility related question on SSP questionnaire at BL, M4(DTI)/M5(OLI), and M12 (DTI)/M13(OLI) • Summary of SSI findings from SSP at M4(DTI)/M5(OLI), and M12 (DTI)/M13(OLI) • Proportion of SSPs and PSPs that respond in agreement on relevant items on the Implementation science questionnaire (ISQ) that each implementation tool and strategy is fit for use through M13 and M12(DTI)/M13(OLI), respectively, and by study arm, clinic characteristics and patient subgroups.

Objectives	Endpoints
	• PSPs perceptions of utility of implementation tools and strategies through SSIs through M13 and by patient subgroups
• To evaluate fidelity to injection and dosing window across traditional and non-traditional settings.	• Proportion of injections occurring within target window from target date (±7 days of target date) through M13 across all arms. • PSPs perception of barriers and facilitators to fidelity to injections window as assessed by SSIs at BL and M12(DTI)/M13(OLI) and surveys at BL, M4(DTI)/M5(OLI), and M12(DTI)/M13(OLI) • SSPs perception of barriers and facilitators to fidelity to injection windows as assessed by SSIs at BL and M12(DTI)/M13(OLI) and surveys at BL, M4(DTI)/M5(OLI), and M12, and implementation monitoring calls (IMC) • Proportion of PSPs completing target number of injections through M13 and by patient subgroups
• To evaluate SSP's and PSP's perceptions, barriers, and facilitators to implementation.	• Summary of SSP and PSP questionnaires related to barriers, facilitators, concerns, and perceptions at BL, M4(DTI)/M5(OLI), and M12(DTI)/M13(DTI). • SSPs perception of which facilitators and barriers to implementation as assessed by SSI at M4(DTI)/M5(OLI) and M12(DTI)/M13(DTI), and IMC. • PSP perception of which facilitators and barriers to implementation as assessed by SSI at BL and M12(DTI)/M13(DTI).
• To evaluate feasibility and acceptability of APRETUDE by SSP and PSP	• Acceptability of Intervention Measure (AIM) and FIM at BL, M4(DTI)/M5(OLI), and M12(DTI)/M13(OLI) • Summary of SSP and PSP questionnaires related to feasibility

Objectives	Endpoints
	and acceptability at BL, M4(DTI)/M5(OLI), and M12(DTI)/M13(OLI) • SSPs reasons for feasibility acceptability as assessed by SSI at M4 and M12(DTI)/M13(OLI) • PSP reasons for feasibility acceptability as assessed by SSI at BL and M12(DTI)/M13(OLI)
• To evaluate the use of oral CAB as oral lead-in by participants and providers.	• Proportion of PSPs that have oral lead-in before CAB injection. • Proportion of SSPs that choose oral lead-in before CAB injection. • SSPs perception on reasons for decision to use oral lead-in through SSI and survey at BL, M4(DTI)/M5(OLI) and M12(DTI)/M13(OLI). • PSPs perception on reasons for decision to use oral lead-in through SSIs and surveys at BL
• To evaluate switch from oral PrEP to APRETUDE	• Proportion of PSPs that complete a sexual health assessment and start APRETUDE through M13 ○ Current oral PrEP users ○ Former oral PrEP users ○ Never used oral PrEP • PSPs reasons for choosing APRETUDE, including switching, as assessed by SSIs and ISQ
Other / Tertiary	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	
If the site has only DTI patients, endpoints will be a month prior for SSPs	

4. RESEARCH DESIGN

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

4.1. Study Design

4.1.1. Randomization and Blinding

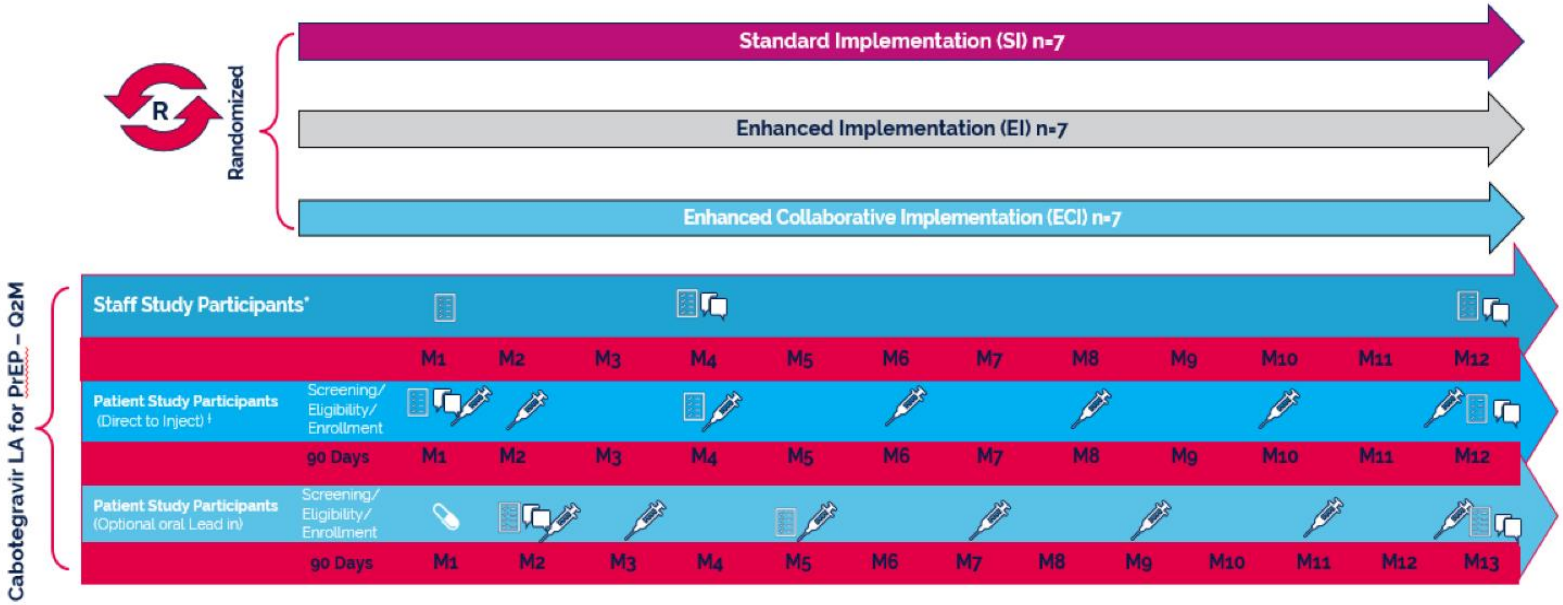
This study is being conducted following FDA approval and commercial availability of CAB PrEP in the U.S. Approximately 21 clinics located in EHE jurisdictions will be randomized 1:1:1 across the three implementation conditions. Randomization will occur at the level of clinical study sites. Sites will be stratified by clinic type, e.g., women's health, general primary care, trans health. The study team will enroll the staff (approximately 35 per arm) at the study site (who will be enrolled as "Staff Study Participants" (SSPs). Approximately 250 adult Black cis-and-transgender women who recently tested negative for HIV at the clinical sites will be enrolled by their PrEP provider across the 21 clinical sites.

Clinics randomized to SI will have access to the standard toolkits for providers and patients that will be available for APRETUDE to use as needed. Clinics randomized to EI will receive enhanced toolkits for providers and patients, a patient-provider assessment to be completed with patients during clinical visits, and a robust provider education on HIV and PrEP. Clinics randomized to ECI will receive enhanced toolkits for providers and patients, a patient-provider assessment to be completed by patients prior to clinical visits, and robust patient and provider education on HIV and PrEP. No study participants will be blinded, and all will be aware of the intervention conditions.

Implementation science methodology using both quantitative and qualitative measures will be used to assess whether EI and ECI as opposed to SI results in higher perceptions of appropriateness of CAB PrEP for Black cisgender women and TGW. The study will also evaluate adoption, feasibility, fidelity to, and acceptability of the implementation strategies and CAB PrEP; and identify barriers and facilitators to implementation. The implementation outcomes will be assessed from the perspectives of individuals receiving CAB PrEP who are enrolled as "Patient Study Participants" (PSPs) and the SSPs (see below for definitions of participants). Clinical data will be collected from PSPs to monitor safety and efficacy (Section 8 to Section 10).

See Figure 1 for the study design schematic.

Figure 1. Study Design Schematic



- Staff Baseline assessments are conducted before the enrollment of the first participant.
- †N=250 PSP baseline assessment are completed on or before Dose 1 of CAB LA for PrEP injection.

SURVEYS=QUANTATIVE (numbers for analysis)
INTERVIEWS=QUALITATIVE (words for analysis)

4.2. Study Population

There are two types of participants in the study:

- "Patient Study Participants" (PSPs) will refer to individuals who are enrolled in the study and who will receive commercially available CAB PrEP via prescription from the PrEP provider (see below) at the corresponding site. PSPs will be monitored according to usual standard care for CAB PrEP recipients at the PrEP provider's discretion.
- "Staff Study Participants" (SSPs) will refer to site staff who are involved in administrative and clinical aspects of offering and administering PrEP to PSPs and participate in the staff study assessments. SSPs may include healthcare providers, nurses, staff performing injections, clinic administrators, pharmacists, and laboratory staff (if labs are being done on site).

The staff who will be recruited for participation in the study as SSPs will vary by site size, site structure, site workflow and staffing structure. As SSPs, they will complete implementation assessments on the implementation strategies at their site. At a minimum, SSPs at each site will include at least one qualified personnel (referred as "PrEP provider") who will prescribe PrEP regimens, including CAB PrEP, and be responsible for standard of care clinical management and protocol-specified assessments for PSPs during the duration of the study (Section 8 to Section 10).

Eligible and consenting PSPs will be followed for 12 months from the time of enrollment and receipt of the first administration of CAB tablets for PrEP oral lead in or APRETUDE (for direct to injection PSPs). The study includes a screening period of up to 90 days to allow sufficient time for any benefit verification checks to be completed, as required. PSPs will be initiated on CAB PrEP as soon as their eligibility is confirmed.

Clinical staff who are important to CAB LA delivery within each site will be included as SSPs. Consenting SSPs at the investigator site will be asked to participate in the implementation strategies as delineated in each arm of the study as well as the quantitative and qualitative study assessments to evaluate the impact of the three implementation strategy conditions on the perception of the appropriateness of APRETUDE. For a detailed Schedule of Activities (SoA) refer to ANNEX 1. CAB dosing adherence information and schematics can be found in the Study Reference Manual (SRM).

Approximately 250 HIV negative PSPs will be enrolled to receive APRETUDE and implementation strategies as delineated by arm. We aim for a minimum of 20% and no more than 30% of the enrolled PSPs to be TGW.

Approximately 105 SSPs will be enrolled in the study. The number of SSPs will vary by site and approximately five per site will be included**.** These will include but not be limited to physicians, nurses, medical assistants, pharmacists, front desk staff, case managers and others that may be involved in the APRETUDE clinic implementation. During the screening period, PSPs who enroll into the study will complete informed consent and confirmation of inclusion and exclusion criteria will be conducted.

SSPs will be selected in advance of the investigator meeting and will be enrolled and assigned an SSP number (refer to the SRM for details) around the time of the site initiation visit, prior to the site's first participant visit.

4.2.1. Eligibility Criteria

4.2.1.1. Inclusion Criteria for PSP

Age:

1. Participant must be ≥18 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. HIV negative at screening. Type of HIV-1 test is per standard of care. NOTE: A negative HIV-1 test must be documented ≤7 days prior to the initiation of CAB PrEP. If the participant was confirmed to be HIV negative >7 days prior to initiation of CAB PrEP, repeat the HIV-1 test and reconfirm that the participant is HIV negative.
3. No prior history of receiving oral CAB or CAB LA injections (Note: prior or active use of non-CAB PrEP (TDF/FTC or TAF/FTC) at screening is allowed).
4. PrEP provider deems CAB PrEP use to be appropriate per the applicable CAB PrEP prescribing information prior to enrollment in the study.

Sex

5. Female at birth or self-identified Transgender Female.

Race

6. Self-identified as African American/Black

Informed Consent

7. Capable of giving signed informed consent as described in Section 7.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

4.2.1.2. Exclusion Criteria for PSP

Medical Conditions

HIV indeterminate or positive test result during screening.

Prior/Concurrent Clinical Study Experience

A participant of concurrent interventional clinical or implementation science study at any time during the study

Other exclusions

1. Cis-gender or Transgender male
2. As dictated in the Prescribing Information in consultation with the prescriber.

4.2.1.3. Inclusion Criteria for SSPs

An SSP will be eligible for inclusion in this study if:

1. They are site employees responsible for administrative (for administrative SSPs)/ or clinical (for clinical SSPs) aspects of implementing and administering CAB PrEP at the site.
2. Has the required qualifications according to their role and delegated the appropriate responsibilities by the investigator.
3. Be able to understand and comply with protocol requirements, instructions, and restrictions.
4. Understand the long-term commitment to the study, have adequate resource to complete assessments for the duration of the study at the point of enrollment.

4.2.1.4. Exclusion Criteria for SSPs

An SSP will be ineligible for inclusion in this study if:

1. Engaged or planned engagement in an implementation science study with **similar strategies** on long-acting **PrEP** injectables at any time during the study. SSP does not have adequate resource to complete study assessments.

4.3. Study Groups and Duration

This study will include the following groups: Cisgender and transgender women who are HIV negative and clinical staff at clinical sites offering PrEP. PrEP sites will be randomized to SI, EI, ECI prior to PSPs and SSPs, enrollment.

Assessments can be found in ANNEX 1 and ANNEX 2.

4.3.1. PSPs - Clinical Considerations

Cisgender and transgender women who are HIV negative prior to initiation of CAB PrEP who have either not previously received PrEP (i.e., PrEP naïve) or that are current or prior users of oral PrEP (e.g., Truvada, Descovy, generic TDF/TFC) or who meet CDC eligibility for PrEP initiation are allowed in the study.

Administration of CAB PrEP will be in accordance with the prescribing information in the US. PSPs will either receive or not receive optional oral lead-in (OLI) of CAB PrEP prior to their first APRETUDE IM injection based on participant or PrEP provider preference, which will be recorded in the eCRF. PSPs who receive optional OLI should receive oral CAB tablets for PrEP for approximately 1 month (at least 28 days) prior to their first injection of APRETUDE.

The sexual health assessments will be completed after required privacy confirmations are conducted but could occur before formal study informed consent. Participants meeting all eligibility criteria at the screening visit will sign the informed consent form at the PrEP site and will enter the study. For participants receiving OLI, the final dose should be taken on the same day as the IM injections are started. Dosing will be done in accordance with CAB LA prescribing information. The sexual health assessments will be completed after required privacy confirmations are conducted but could occur before formal study informed consent.

A minimum set of screen failure information will be collected including demography, screen failure details, eligibility criteria, and any serious adverse events. Individuals who do not meet the criteria for participation in this study (screen failure) or whose insurance plan takes more than 90 days to approve APRETUDE may be rescreened one time within 12 weeks of the original screening; informed consent will need to be reviewed and re-signed for each rescreen. Participants will be issued a new ID number for every screening/re-screening event. SSPs will not be captured for screen failure reporting.

If a PSP plans to miss the injections by more than 7 days from a scheduled APRETUDE injection, then in consultation with the PrEP provider, CAB tablets for PrEP may be taken daily until the PSP restarts IM injections as per the US prescribing information for CAB PrEP and within the study's time period. For oral PrEP duration greater than two months, the decision to use other recommended oral PrEP regimens (Saag, 2020) in this clinical setting will be made by the PrEP provider. Dosing of oral PrEP regimen used in such cases of missed APRETUDE injections will be recorded in the eCRF. ViiV is not supplying APRETUDE to the participants in this study. However, oral APRETUDE is

provided through commercial means and will be consistent for the study in the event of oral bridging.

The total study duration for PSPs is approximately 12 months from the time of enrollment and receipt of the first administration of APRETUDE IM injections. A participant is considered to have completed the study if he/she has finished all Month 12 assessments and receive their last injections of APRETUDE.

4.3.2. SSPs - Clinical responsibilities

SSPs will complete assessments as outlined in ANNEX 1 and agree to data privacy requirements prior to the completion of study assessments. Assessments will include surveys and interviews at baseline, M4 and M12; baseline surveys with SSPs should be completed prior to the enrollment of the first participant at their site. Sites in the EI arm will participate in quarterly group and monthly one-on-one facilitation calls. The PrEP provider at the site will manage and remain responsible for all clinical aspects of the PSPs enrolled at the site during the study.

- During the Screening Period, the site will obtain the PSP's informed consent and confirm inclusion and exclusion criteria prior to enrolling in the study/Day1. The site will also complete demography and vital signs and required labs per clinical local standard of care.
- See SoAs for specific laboratory test results that should be documented in the eCRF, e.g., all HIV testing types and results and any positive STI clinical diagnoses (defined for this study as syphilis (any stage), gonorrhea, chlamydia,or trichomonas) at screening and at any time point during the study, laboratory abnormalities associated with AEs leading to study discontinuations, positive pregnancy test results). The site will explain to the PSPs that medical records may be requested from other medical facilities to support complete reporting of SAEs or other events if they occur during the study.
- For PSPs diagnosed with incident HIV-1 infections (defined as newly diagnosed HIV infection following enrollment and during the study), the site may perform additional tests, including but not limited to HIV-1 viral load, CD4 count, genotype/phenotype tests, and recency assays (where available), and initiate antiretroviral therapy (ART) as per the site's standard of care. See SoA for collection of available results as well as the start date of ART and classes of ART regimen used for PSPs with incident HIV-1 infection.
- The PrEP provider at the site will prescribe CAB tablets for PrEP to PSPs who will receive optional OLI and administer APRETUDE IM injections as per approved prescribing information.
- The site will be responsible for scheduling every two months injections, reminding participants when they are scheduled to receive their injections, and rescheduling missed injections.
- The PrEP provider will be notified that CRO staff and/or the Medical Monitor may request additional information, including medical records if required, on AEs and

SAEs assessed by the investigator as related to CAB PrEP, or other assessments (e.g., pregnancies).

- The PrEP provider will monitor all visits (planned, missed, and any unplanned visits) and will determine when to start oral PrEP for planned missed doses, or to restart APRETUDE according to the USPI.
- If the PrEP provider cannot contact the PSP following missed injections of APRETUDE and a PSP misses two consecutive scheduled APRETUDE injections, this should be documented in the participants medical record and they will be discontinued from the study.

Optional oral lead-in (OLI), every injection visit and if applicable, early discontinuation, should be recorded as a study visit in the PSP medical record and the eCRF. Additional PSP contacts should be documented in the medical records but will not need to be entered into the CRF.

The site is responsible for the completion of all data entry accurately transcribed from the source documentation in the PSPs medical records, including the reporting of AEs and SAEs assessed by the PrEP Provider as related to CAB PrEP. (See Section 10.3 for additional information). All study assessments and events should be kept in the PSP source documentation (refer to Section 12.7.4).

Total duration of study participation for SSPs is approximately 12 months from the time of enrollment/ Day 1 of the last PSP at their site (surveys and monthly injections). In the event of turnover in SSPs, replacement staff will undergo study training and continue staff study activities per SOA. The number of SSPs will vary by site and will be approximately 5 per site.

5. IMPLEMENTATION RESEARCH METHODS

5.1. Study Arms Overview

Clinics receiving SI will receive toolkits that will be available when APRETUDE is commercially available and will meet monthly with the implementation science CRO to report implementation progress and challenges. Clinics receiving EI and ECI support will receive all components of SI support and additional implementation strategies focused on providers and patients. These strategies are outlined in Table 1, Table 2, and Table 3 in terms the dimensions recommended by Proctor and colleagues (Proctor, 2013): action, actor, action targets, dose, outcomes, and justification.

5.1.1. Standard Implementation

The SI arm receives the standard toolkits that are anticipated to be available for APRETUDE and will have access to the GSK Response Centre, an optional product information resource for patients and providers. Details on the strategies provided to clinics randomize to SI are provided in Table 1. In preparation for the study, all SSPs will attend the study investigator meeting, where they will receive information on safety and effectiveness of APRETUDE and study procedures. Clinics randomized to the SI arm will receive monthly implementation monitoring to evaluate implementation progress and assess barriers to implementation throughout the study.

Table 1 Standard Implementation Strategies

	Toolkits	Implementation Monitoring	GSK Response Center
Study Arm	SI, EI, ECI	SI, EI, ECI	SI, EI, ECI
Action	Injection education video, Instructions for use, Dosing and administration guide, Adherence checklist, Implementation video, Demo packs, Patient appointment reminder card	Brief virtual meetings between IS CRO and implementation lead at each study site to discuss implementation progress	Nurse ambassadors for patients and support for clinicians available through a call center
Actor	ViiV developed, delivered with support of study team	IS CRO	GSK Response Center
Action target	Improved provider knowledge	IS CRO knowledge on implementation progress	Patient and provider knowledge, provider self-efficacy for injection delivery and resolving post injection concerns
Dose	Available to be used as needed	Monthly (up to 30 minutes), throughout the study	Available to be used as needed

	Toolkits	Implementation Monitoring	GSK Response Center
Outcome	Feasibility, acceptability	Sustainability, scale up	Feasibility, acceptability
Justification	Provide logistic support to integrate new modality into clinics	Calls will be used to collect information that can be used to develop lessons-learned to promote sustainability and scale-up in future clinics	Information and support available to patients and providers on an as-needed basis

SSPs and PSPs will complete all assessments per the SoA (ANNEX 1).

5.1.2. Enhanced Implementation

The EI arm will receive all components of SI arm and additional provider-focused implementation strategies. Provider-focused strategies will include a PrEP Options Communication Tool, Provider Education, and ViiV Connect enhanced support (see Table 2).

The *PrEP Options Communication Tool* is a visual tool that providers will use with the patient during the visit to discuss patients' eligibility for PrEP and options for oral and injectable PrEP. Providers in clinics in the EI arm will be asked to use the *PrEP Options Communication Tool* as part of routine practice with all Black women who are patients at the clinic and not to limit the use of the tool with only patients who are enrolled in the study. Provider Education will include modules related to medical mistrust, comfort and facilitating discussion on sexual health, women's health, transgender health, HIV, and APRETUDE. The ViiV Connect enhanced support will provide educational tools to address challenges related to the insurance verification.

Table 2. Enhanced Implementation Strategies

	PrEP Options Communication Tool	Provider Education	ViiV Connect Enhanced Support
Study Arm	EI	EI, ECI	EI
Action	Clinicians use the *PrEP Options Communication Tool* in clinical encounter with patient to discuss patients' appropriateness for PrEP	Comprehensive training to educate providers about PrEP, including long-acting Cabotegravir; highlight considerations for providing PrEP to Black cisgender and transgender women; and	Clinics will have access to a ViiV Connect educational video, tailored education on insurance verification, guidance documents to help support

	PrEP Options Communication Tool	Provider Education	ViiV Connect Enhanced Support
		address providers' concern; and guide providers' implementation of PrEP into their practice.	insurance verification
Actor	Clinicians at site in EI arm	IS Vendor	ViiV Connect
Action target	Provider knowledge of patient appropriateness for PrEP	Providers' PrEP knowledge Providers' self-efficacy to provide CAB LA health, HIV, and APRETUDE.	Provider knowledge of ViiV connect process
Dose	At clinical visits	Up to 8 modules, totally about 3 hours total	Educational materials, guidance documents monthly, video on demand
Outcome	Adoption of APRETUDE, Appropriateness	Appropriateness, acceptability	Adoption
Justification	Clinicians need knowledge of how to discuss treatment options with patients and make prescribing decisions with patients	Data related to the use of the training will provide evidence for the utility of a PrEP training for the provision and future scale-up.	Addresses a key barrier to initiating treatment by provides information to support the insurance verification process

5.1.3. Enhanced Collaborative Implementation

The ECI arm will involve implementation strategies to support patient activation and provider awareness. Clinics randomized to ECI will receive all components of SI and

additional implementation strategies to support patient activation and ensure provider awareness. ECI strategies will include a patient Assessment Tool and Readiness Tools, Provider Education, Persistence Support, and PrEP Ambassadors (see Table 3).

Patient Assessment and Readiness Tools will be available to patients who receive care in clinics randomized to the ECI arm. The tool will be available to patients as part of routine practice and will not be limited to patients enrolled in the study. Patients will complete a sexual health assessment as part of this tool prior to their visit with the provider to help patients understand their eligibility for PrEP and assess their readiness to begin PrEP. The Readiness portion of the tool will include access to brief educational videos to increase awareness of HIV and understand the benefits of PrEP. Patients enrolled in the study will have access to Persistence Support in the form of messages and reminders to keep patients motivated and they will also be able to contact PrEP Ambassadors with any questions or to discuss any questions about PrEP. Providers in the ECI arm will receive Provider Education to ensure they are prepared to discuss PrEP treatment options with patients. SSPs and PSPs will complete all assessments per the SoA (ANNEX 1).

Table 3. Enhanced Collaborative Implementation (ECI) Strategies

	Patient Assessment and Readiness Tools	Provider Education	Persistence Support	PrEP Ambassadors
Study Arm	ECI	EI, ECI	ECI	ECI
Action	Patient completes sexual health assessment prior to the clinical visit to self-assess readiness, and can view educational videos, the provider will have access to the results of this tool using a web-based application	Comprehensive training to educate providers about PrEP, including long-acting Cabotegravir; highlight considerations for providing PrEP to Black cisgender and transgender women; and address providers' concern; and guide providers' implementation of PrEP into their practice.	Digital support to keeping patients motivated when they face competing priorities, may include earning points or incentives for completion of their goals	Ambassadors will be available virtually to discuss treatment decisions and share their experience with PrEP
Actor	Patient	IS Vendor	Patient	PrEP Ambassador
Action target	Patient knowledge and readiness	Providers' PrEP knowledge Providers' self-efficacy to provide CAB LA	Patient persistence	Patient readiness, activation, and persistence
Dose	1x (4-6 minutes)	Up to 8 modules, totally about 3 hours total	Monthly (3-5 minutes)	Available to be used as needed
Outcome	Patient acceptability	Appropriateness, acceptability	Fidelity	Patient acceptability, appropriateness, fidelity
Justification	Tool will increase patients' knowledge and readiness for change prior to meeting with their provider	Data related to the use of the training will provide evidence for the utility of a PrEP training for the provision and future scale-up	Support to encourage patients to maintain focus on the goals established using the readiness tool	Ambassadors will provide social support, share knowledge and experience

5.1.4. Implementation Assessments

Implementation outcomes align with the study's objectives and Proctor and colleagues' (Proctor, 2011) implementation outcome recommendations. Implementation assessments are as outlined in Table 4. For SSPs, baseline assessments should be completed prior to the enrollment of first patient study participant. Implementation information may also be gathered from or about site staff members who are administering APRETUDE to non-PSPs.

One or more interim analysis will be conducted to provide early evaluation of the implementation science primary and key secondary objectives. The timing of the interim/s will be based on when a sufficient number of SSPs and/or PSPs surveys and interviews have been completed.

Table 4. Implementation Assessments

Outcome	Assessment Level	Measurement	DTI/OLI Time point[2]	Dosing Equivalent
Appropriateness- CAB PrEP	Staff Study Participants	IAM, questionnaires	BL, M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	
		SSI	M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	
	Patient Study Participants	IAM, questionnaires	BL, M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	D1, D3, D7
Adoption - PrEP Assessment	Clinic Level	Proportion of Black women who complete sexual health assessment	Monthly	
Adoption - CAB PrEP	Clinic Level	Proportion of Black women who initiate CAB LA	Monthly	
Feasibility - Implementation Strategies	Staff Study Participants	FIM, questionnaires	BL, M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	

Outcome	Assessment Level	Measurement	DTI/OLI Time point[2]	Dosing Equivalent
		SSI	M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	
Acceptability	Staff Study Participants	AIM, survey, and SSI		
Acceptability	Participants	AIM, questionnaires, and SSI		
Fidelity - CAB PrEP Dosing	Clinic Level	Adherence to Target date (±7 days), eCRF	Monthly	
		Use of oral bridging	Monthly	
	Patient Study Participants	Patient Survey	BL, M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	D1, D3, D7
	Staff Study Participants	Staff Survey	BL, M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	
		SSI	M4, M12	
		# clinical staff-initiated assessments/ # eligible pts	Monthly	
Perceptions, barriers & facilitators - CAB PrEP Implementation	Staff Study Participants,	Staff Survey	BL, M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	
		SSI	M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	

Outcome	Assessment Level	Measurement	DTI/OLI Time point[2]	Dosing Equivalent
	Patient Study Participants	Patient Survey	BL, M4(DTI)/ M5(OLI), M12(DTI)/ M13(OLI)	D1, D3, D7
CCI [redacted]				

Abbreviations: FIM: Feasibility of Intervention Measure; IAM: Appropriateness of Intervention Measure; SSI: Semi-Structured Interviews; M: Month; D: Dose;

*Composite measure to be develop in consultation with stats; example of measures provided

[1]Measures taken from both SSPs and PSPs across the study implementation period; to be further refined

[2] For SSPs, Baseline assessments should be completed prior to the enrollment of first patient study participant

5.1.4.1. Timepoint Definitions for Completion of Surveys and Interviews

Patient Study Participants:

PSPs:

- PSPs who are started on oral CAB PrEP as optional OLI will receive their first dose of oral CAB on Study Day 1. PSPs who are started on APRETUDE injections (direct to inject) will receive their first dose of APRETUDE injection on Study Day 1.
- Each administration of APRETUDE injection will be categorized by the sequential number, e.g., for DTI PSPs; Dose 1 (first injection), Dose 2 (second injection) for OLI PSPs; Dose 1 (first oral dose), Dose 2 (first injection) and the corresponding Study Month will be recorded.
- Baseline IS assessment is defined as the first assessment taken on or before receiving Dose 1 of APRETUDE injection. Baseline questionnaires should be completed within three weeks prior to or on their Dose 1 visit and before receiving the first APRETUDE injections.
- Participants M4 (DTI)/M5(OLI) questionnaires and M12 (DTI)/M13(OLI) questionnaires and interviews should be completed within 2 weeks before or 2 weeks following study visit.

- All study visits, including those where surveys and/or interviews are administered at M4(DTI)/ M5(OLI) and M12(DTI)/ M13(OLI), will be anchored off of each PSP Dose 1 visit, so it reflects months in study, regardless of what dose they are on and regardless of whether they have missed any injections and received oral CAB tablets for PrEP.
- For each PSP, the last APRETUDE injection is to occur at the last study visit.
- Approximately 3 PSPs per site will participate in SSIs; number of SSIs might vary by site. Additional PSP contacts should be documented in the medical records but will not need to be entered as a study visit in the eCRF, unless the contact results in any safety information that is required to be documented for the study (refer to Section 9).
- Qualitative Interviews will be conducted with all PSPs who discontinue participation within one month of discontinuation, when possible.

Study Staff Participants:

- Baseline for each site is defined when the first participant enrolls into the study at that specific site and the participant is administered the first IM injection.
- Baseline surveys and interviews should be completed by all SSPs prior to the first injection of the first participant at each PrEP site.
- Baseline for each site is defined when the PSP participant enrolls into the study at that specific PrEP site and the PSP is administered the first IM injection.
- Month 4 visit and Month 12 visit will be defined after at least 1 PSP, at their respective PrEP site, has completed their Dose 3 visit or Dose 7 study visit, respectively.
  - Surveys and/or interviews can be completed within 2 weeks of Month 4 and Month 12
  - For sites with both OLI and DTI participants, M4/M5 visit will be defined when at least 1 participant, at their respective site, has completed their M4(DTI)/M5(OLI) study visit (Dose 3 visit), respectively, whichever comes first. M12/M13 visit will be defined after at least 1 participant, at their respective site, has completed their M12(DTI)/M13(OLI) study visit (Dose 7 visit), whichever comes first.
  - For a site with only DTI patients, the visits will be defined at M4 and M12, respectively. For a site with only OLI patients, the visits will be defined at M5 and M13, respectively.
  - Baseline questionnaires with SSPs should be completed prior to the enrollment of the first participant at their site, which might vary by site

depending on whether the first PSP started CAB PrEP with or without optional OLI.

Implementation Monitoring:

- Clinics in all arms will identify two staff members who will be able to share knowledge about patients and staff experience throughout the study and will be available to participate in calls at regular intervals. At least one consistent SSP from each site should participate in all implementation monitoring. This SSP should be aware of how implementation is going and be willing and able to report out on behalf of the clinic and communicate back to the team at the clinic.
- Selected SSPs will attend brief monthly calls (up to 30 minutes) for the first twelve months of the study or to an agreed upon end point in consultation with the implementation science lead and clinical site. During each call, SSP will be asked to report on the status on their implementation efforts, any key changes in their clinic that may impact implementation efforts, any barriers they have encountered, and what actions they have taken to address these challenges.
- Data from IMC will be used to monitor implementation milestones and track implementation barriers over time.

5.1.5. Primary Endpoint

The primary endpoint is to evaluate SSP perception of the appropriateness of APRETUDE for Black women using the Intervention Appropriateness Measure (Weiner, 2017) score at M12(DTI)/ M13(OLI). The secondary implementation endpoints include the appropriateness of APRETUDE for PSP, the adoption of APRETUDE (SSP), the feasibility and acceptability of implementation strategies (SSP), and fidelity to injection and dosing window. Quantitative and qualitative data as well as implementation monitoring data will be triangulated to inform final study results.

5.2. Scientific Rationale for Study Design and Research Methods

The HPTN 083 and 084 studies found CAB LA statistically superior to oral PrEP at preventing HIV acquisition in transgender women as well as cisgender women. Yet, clinical efficacy of a product often fails to translate to real-world effectiveness, including awareness, knowledge, demand, acceptability and use. Research shows that just because an effective treatment exists, translation into routine care can be slow and often never occurs (Bauer, 2020). For long acting injectables for HIV prevention, however, early acceptability research has shown preference for an injectable prevention method over other methods by end-users (Philbin, 2021; Tolley, 2020). However, as the first injectable HIV prevention modality, CAB LA will require changes to the current routine of prescribing oral PrEP therapy, including but not limited to workflow, staffing needs, delivery platform considerations, and training needs (Pleuhs, 2020). Therefore, implementation research will be used to identify and understand the strategies that will

enhance the delivery and/or integration of CAB LA into existing and new PrEP delivery systems and programs is critical to its access and use.

Implementation research focuses on systematic uptake of research findings into routine practice to improve health services. The study will be guided by a set of evidence-based implementation frameworks to ensure the robustness of the research. Implementation outcomes will be identified and measured at the service and patient level to determine how effectively and efficiently CAB LA is being integrated and delivered within the identified clinics. The study will identify the barriers and facilitators to effective implementation while allowing for the tailoring and adapting of strategies to fit the needs of each clinical setting. As a result, this proposal is guided by frameworks that are appropriate to the proposed stage of implementation research, including both a process and determinants framework and an outcomes taxonomy.

5.2.1. Implementation Frameworks

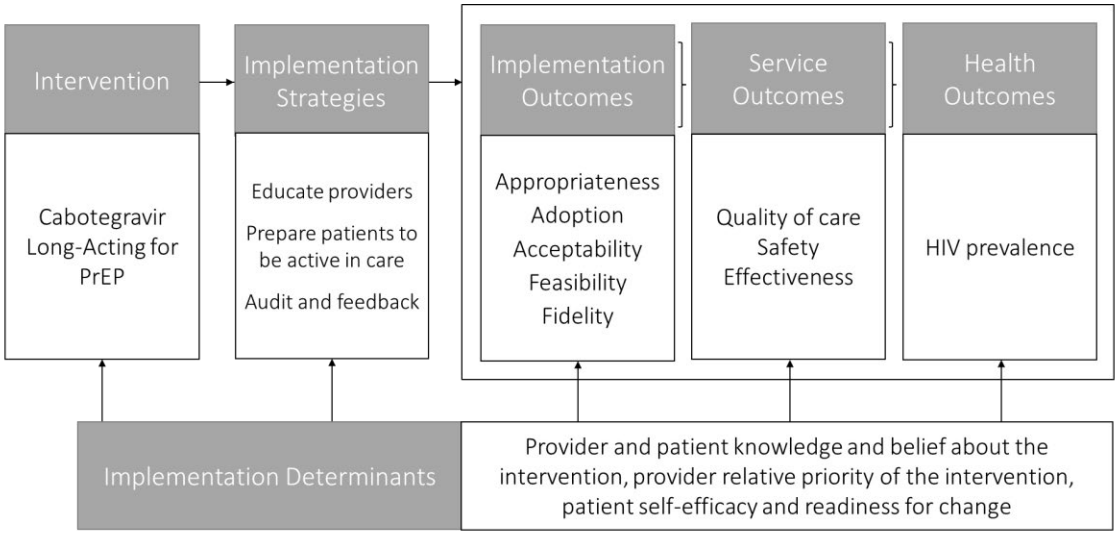
The study is guided by implementation science frameworks (covering evaluation, determinants, and process): the Proctor (Proctor, 2011) outcomes framework the Consolidated Framework for Implementation Research (CFIR) (Damschroder, 2009).

The Proctor outcomes framework will provide guidance on study design and outcomes (Proctor2011). The framework distinguishes between three distinct but interrelated types of outcomes – implementation, services, and client health outcomes. Improvements in client health outcomes (e.g., remaining HIV negative) and service outcomes (e.g., on-time CAB LA injections) are impacted by the implementation process and implementation outcomes. The framework will be used to guide measurement decisions for the key outcomes that will be assessed: feasibility, fidelity, acceptability, and reach.

The Consolidated Framework for Implementation Research (CFIR) will be integrated with the Proctor outcomes framework to serve as the outcomes and determinant's framework. CFIR provides a repository of standardized implementation-related constructs organized across five major domains that influence implementation and implementation effectiveness - intervention characteristics, outer setting, inner setting, characteristics of individuals involved, and the process of implementation.

Figure 2 shows the implementation determinants, strategies, and outcomes of interest for this study. The primary implementation determinants this study seeks to address are lack of patient and provider knowledge about CAB LA, low patient self-efficacy related to discussing treatment options with their provider, lack of patient readiness to initiate CAB LA, and the degree to which providers are prioritizing sexual health assessments, conversations related to PrEP, and prescribing PrEP when indicated. We will use several implementation strategies to address these determinants with a focus on patient a provider education, and strategies to increase patient and provider awareness. These strategies will target perceived appropriateness, feasibility and acceptability of CAB LA, the adoption of CAB LA, and fidelity to treatment.

Figure 2 Proctor & CFIR Integration Application



Adapted from Proctor, E. K., Landsverk, J., Aarons, G., Chambers, D., Glisson, C., & Mittman, B. (2009). Implementation research in mental health services: an emerging science with conceptual, methodological, and training challenges. Administration and Policy in Mental Health and Mental Health Services Research, 36(1), 24-34.

6. STATISTICAL CONSIDERATIONS

6.1. Statistical Hypotheses

The study will examine the impact of the SI, EI, ECI on the delivery of CAB PrEP in clinical sites serving Black cisgender women and TGW. It is anticipated that EI and ECI strategies will have a higher impact compared to SI. The hypothesis of this study is that Enhanced Implementation (EI) or Enhanced Collaborative Implementation (ECI) strategies will have a significant effect compared to standard implementation (SI) in terms of mean staff study participant (SSP) IAM score at M12(DTI)/ M13(OLI). The following two hypotheses will be tested:

$$H_{01}: \mu_{EI} = \mu_{SI} \qquad H_{11}: \mu_{EI} \neq \mu_{SI},$$

$$H_{02}: \mu_{ECI} = \mu_{SI} \qquad H_{12}: \mu_{ECI} \neq \mu_{SI}$$

This is a multi-arm trial with two pairwise comparisons but given the nature of the study (low interventional study; the intervention is the implementation strategy and not the drug and there is no new indication) there will be no adjustment for multiple comparisons. It is anticipated that EI and ECI strategies will have a higher impact compared to SI. Implementation strategy recommendations arising from this study will be based on both clinical and statistical significance and may be based on secondary outcomes and/or safety outcomes as well as primary outcomes. Statistical evidence from a set of primary null hypotheses may not be sufficient to lead to recommendation in clinical practice. There is a need to consider the totality of the evidence in favour of implementation strategies.

6.2. Study Size

The study size is based on practical considerations in terms of feasibility of enrolling an adequate number of sites, as well as staff and PSPs in each implementation strategy.

6.2.1. Sample Size for Staff Study Participants

The primary endpoint is the SSPs mean Intervention Appropriateness Measure (IAM) score at M12 when comparing Enhanced Implementation to Standard Implementation or Enhanced Collaborative Implementation to Standard Implementation.

Approximately 21 sites will be randomly assigned to one of three arms, each with its own suite of study implementation strategies. Each arm will have a minimum five SSPs per site, hence there will be approximately a total of 105 evaluable SSPs with 35 SSPs in each implementation strategy arm. Results from previous CAB LA treatment study CUSTOMIZE (209493) have shown that the estimated mean score of IAM for SSPs was 4.61 with standard deviation of 0.5 at M12(DTI)/ M13(OLI). Assuming standard deviation of 0.5, with 7 clinics randomized to each implementation arm and minimum 5 SSPs per site this design has 80% power to detect a difference of 0.34 in the mean score of IAM at M12(DTI)/ M13(OLI) using a two-sided test with an alpha level of 0.05 (Figure 3).

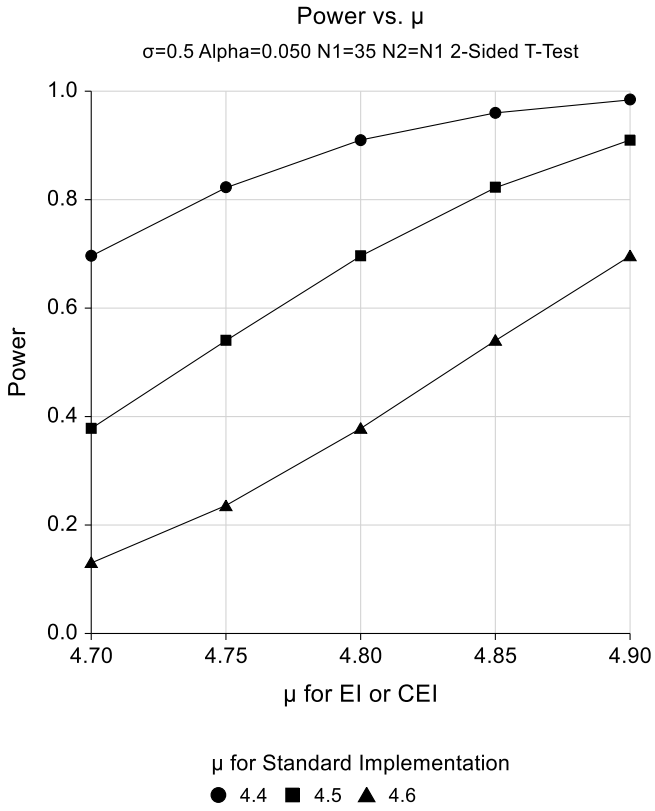
6.2.2. Sample Size for Patient Study Participants

Key secondary endpoint is the PSPs IAM score at M12(DTI)/ M13(OLI) when comparing Enhanced Implementation to Standard Implementation or Enhanced Collaborative Implementation to Standard Implementation. A total of 210 evaluable PSPs at M12(DTI)/ M13(OLI), 70 in each implementation strategy group, produces 80% power at the 0.05 significance level to detect a difference in mean IAM score of 0.24, 0.29 and 0.33 for SD of 0.5, 0.6 and 0.7, respectively. Assuming 15% drop out rate, around 83 participants must be randomized to each implementation strategy to achieve at least 80% power.

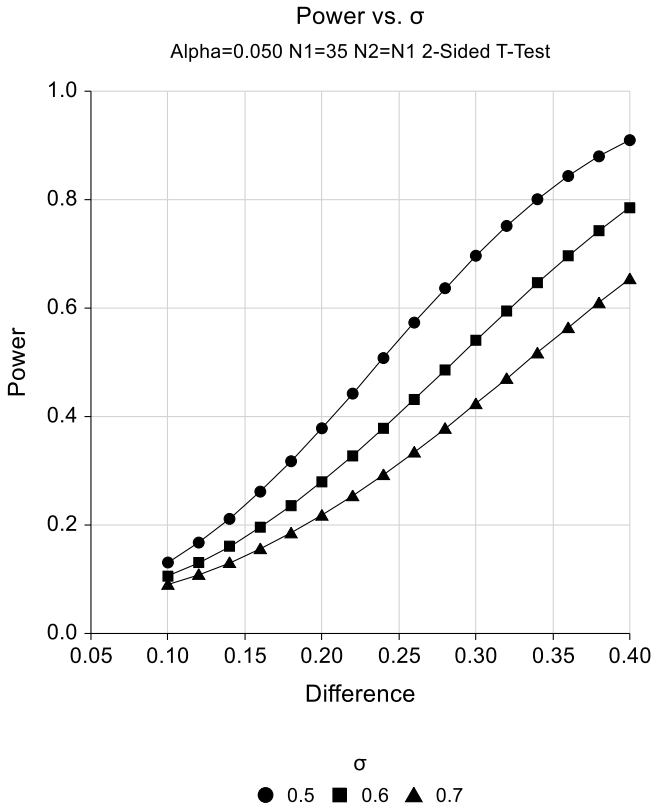
6.2.3. Sample size sensitivity

There is no previous implementation science study conducted with APRETUDE hence to demonstrate the sensitivity of the sample size calculation for the primary endpoint of this study, the following figure presents the power under difference circumstances in terms of the mean (Figure 3a) or standard deviation (Figure 3b), when calculated with a sample size of 35 SSPs per implementation strategy.

Figure 3. Sample Size Sensitivity



a. Power of this study under the assumption of fixed SD of 0.5.



b. Power of this study under different mean difference and SD assumptions.

Power can be further investigated based on standardized effect size d. When comparing the enhanced implementation and standard implementation, d can be defined as the ratio of difference of mean IAM scores between two arms to the standard deviation. Table 5 provides various assumptions of the mean difference, standard deviation, and the relationship to the power. With 35 SSPs per arm, the study will have >=80% power to detect a difference if the effect size is >0.67. Same comparison applies when comparing collaborative enhanced implementation and standard implementation.

Table 5 Power to test difference in IAM between two implementation strategies

Difference in mean at M12	Standard deviation	Effect Size d	Power
0.1	0.5	0.2	0.13
0.1	0.3	0.33	0.28
0.2	0.5	0.4	0.38
0.3	0.7	0.43	0.43
0.4	0.7	0.57	0.65
0.3	0.5	0.6	0.70
0.2	0.3	0.67	0.79
0.4	0.5	0.8	0.91

6.3. Essential Analysis

The primary study objective is listed in Section 3. The hypotheses will be tested at 5% level with a 2-sided test. There will be no sensitivity analyses of the primary endpoint. Because of the cluster randomized study design, observations on individuals in the same cluster are correlated and this correlation needs to be accounted for in the analysis. A linear mixed model methodology will be applied. The IAM score will be the response, and the arm will be the fixed effect. Sites will be entered as a random effect independent of residual error. Estimation will be performed using Restricted Maximum Likelihood, and the null hypothesis of zero mean difference between arms will be tested using a F test. Details on how the data will be analyzed will be described in statistical analysis plan (SAP).

6.4. Secondary Analysis

No multiplicity adjustments for statistical testing of secondary endpoints will be performed. Similarly, as for primary endpoints, random effects models and generalized estimating equations approach will be used to adjust for correlation within the sites due to clustered randomization. All secondary analyses will be described in full in the SAP. Analyses of the implementation outcomes for SSPs and PSPs will use standardized measures, such as the FIM and AIM, as well as items from the ISQ that measure these outcomes using different terminology (Table 6) (Proctor,2011;Weiner,2017;Aarons,2015)

Table 6 Definitions of Implementation Outcomes

Implementation Outcomes	Definition	Additional terminology
Acceptability (Proctor, 2011, Weiner, 2017)	Acceptability is the perception among implementation stakeholders that a given treatment, service, practice, or innovation is agreeable, palatable, or satisfactory	Meets my approval, seems good, meets my needs, is satisfactory, is appealing, I like, I welcome the use of
		Satisfaction with various aspects of the innovation; examples include content, complexity, comfort, delivery, and credibility,
Feasibility Proctor, 2011, Weiner, 2017)	Feasibility is defined as the extent to which a new treatment, or an innovation, can be successfully used or carried out within a given agency or setting.	Practical, realistic, workable, implementable, possible, viable, doable, easy to use, challenging (reverse score)
		Actual fit, suitability for everyday use, convenience*
Appropriateness (Proctor, 2011, Weiner, 2017)	Appropriateness is the perceived fit, relevance, or compatibility of the innovation or evidence-based practice for a given practice setting, provider, or consumer; and/ or perceived fit of the innovation to address a particular issue or problem	Fitting, suitable, reasonable, apt, proper, applicable, well aligned, a good match
		Perceived fit, relevance, compatibility, suitability
Utility (Aarons, 2015)	Seen as being useful and helpful in day-to-day operations and in implementing change and EBP	Useful, helpful
***Convenience is synonymous with published literature terminology and used in this study to measure feasibility**		

CCI

[redacted]

6.6. Interim Analyses

The main analysis will be conducted to evaluate the primary objective of the protocol when all participants have completed their M13 (OLI)/M12(DTI) visit. Other data cuts and analyses may be conducted as necessary to provide early evaluation of the implementation science primary and key secondary objectives, support regulatory submissions and publications. The timing of the baseline or M5(OLI)/M4(DTI) interim analyses will be based on when enough SSPs and/or PSPs have completed their assessments. No adjustment for multiplicity caused by repeated evaluation of the primary endpoint will be made as Baseline and M5(OLI)/M4(DTI) analyses will be secondary.

6.7. Limitations of the Research Methods

Study sample size we will have 80% power to detect a statistically significant difference in IAM score with effect size of >0.67 in both SSP comparisons (EI vs. SI or ECI vs. SI). This is considered a large effect size. In previously reported CAB LA treatment implementation studies, effect sizes were generally small. Nevertheless, this sample size of this study is adequate for assessing the influence of three interventions on perception of the appropriateness and feasibility and to identify any obstacles that need to be addressed for APRETUDE administration.

Study utilizes a cluster randomized design, but an intracluster correlation coefficient (ICC) was not taken into consideration with sample size calculations for the current proposal.

7. PROTECTION OF HUMAN SUBJECTS

7.1. Ethical Approval and Subject Consent

The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to PSPs and SSPs.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to PSPs and SSPs.

The PrEP site will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the PrEP site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

7.2. Participant Confidentiality

7.2.1. PSPs

PSPs will be assigned a unique identifier. Any PSP records or datasets that are transferred to the Sponsor or third party working with the Sponsor to conduct the study will contain the identifier only; PSP names or any information which would make the participant identifiable will not be transferred.

The PSP must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the PSP who will be required to give consent for their data to be used as described in the informed consent.

The PSP must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

All study site staff will ensure protection of PSP personal data and will not include PSPs' names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

7.2.2. SSPs

SSPs will be assigned a unique identifier. Any SSPs datasets that are transferred to the sponsor or third party working with the Sponsor to conduct the study will contain the identifier only; SSP names or any information which would make the SSP identifiable will not be transferred.

SSPs must be informed that their study assessment data will be used by the sponsor in accordance with local data protection law. SSPs will agree to data privacy requirements prior to data collection.

7.3. Informed Consent Process

The PrEP site will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The PrEP site authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

ViiV Healthcare (alone or working with others) may use participant's coded study data and other information to carry out this study; understand the results of this study; learn more about APRETUDE or about the study disease; and publish the results of these research efforts.

The ICF contains a separate section that addresses the use of PSPs for optional further research. The investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

7.4. Quality Control / Study Monitoring

In accordance with applicable regulations including GCP, study monitors will contact the PrEP sites prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and VHC requirements.

When reviewing data collection procedures, the discussion will also include identification, agreement, and documentation of data items for which the eCRF will serve as the source document. The study monitors will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

- The site investigator and the head of the site (where applicable) agrees to allow the monitor direct access to all relevant documents.

8. CAB PREP AND CONCOMITANT THERAPY

The protocol only requires that the PSPs receive marketed CAB tablets for PrEP and APRETUDE, dosed in accordance with the approved label]; no CAB PrEP or any other PrEP will be provided by VHC. No dose reductions, modifications, or changes in the frequency of any components of CAB PrEP, ie, CAB tablet for PrEP or APRETUDE will be allowed during the study beyond what is allowed within the approved CAB PrEP labels.

The PrEP Provider should follow the APRETUDE USPI for the preparation and administration of APRETUDE.

8.1. Missed APRETUDE Injections

Adherence to the APRETUDE injection dosing schedule is strongly recommended. **If a PSP misses a scheduled injection visit, the PrEP Provider should follow the USPI guidance for oral PrEP and schedule for restart of IM injections. The PrEP provider is responsible for all clinical management decision for participants after a missed dose, as described in Section 2.4 of the USPI.**

Any changes in a PSP's CABPrEP regimen must be recorded in the eCRF. This includes CAB tablets for PrEP or other approved oral PrEP to ensure PrEP coverage during a planned or unplanned missed injection visit.

PSPs receiving CAB PrEP may be at risk for acquiring HIV and development of virologic resistance (USPIs for CAB tablets for PrEP and APRETUDE). PrEP providers should refer to the USPI and CDC PrEP guidelines for the appropriate management of incident HIV infection.

8.2. Treatment of an Overdose

For this study, any dose of CAB PrEP greater than listed in the USPI will be considered an overdose. All overdoses and any treatment for the overdosage should be recorded in the eCRF.

There is no known specific treatment for overdose with CAB PrEP. If overdose occurs, monitor the participant, and apply standard supportive treatment as required, including monitoring of vital signs as well as observation of the clinical status of the patient, and record in the participants source documentation. Consider the prolonged exposure to cabotegravir following injections when assessing treatment needs and recovery.

In the event of an overdose, the site must:

1. Take action according to the USPI and notify and consult the primary Medical Monitor.

2. Document the timing and the quantity of the excess dose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the PrEP provider.

8.3. Concomitant Therapy

PrEP providers will monitor concomitant medications per the USPI, especially regarding concomitant medications that are contraindicated with CAB PrEP and medications with a potential for drug-drug interactions with CAB PrEP.

The PrEP provider will note all new concomitant medications and determine if any new contraindicated or concomitant medications with the potential for drug interactions are noted prior to administering CAB PrEP. Contraindicated or concomitant medications with the potential for drug interactions according to the APRETUDE USPI must be recorded in the eCRF at each visit. If the PrEP provider, under the guidance of the USPI, determines that the PSP must discontinue the study due to the necessary administration of a contraindicated medication, then see Section 9 for further instructions.

9. DISCONTINUATION OF CAB PREP AND PARTICIPANT DISCONTINUATIONS

9.1. Discontinuation of CAB PrEP

It may be necessary for a PSP to permanently discontinue CAB PrEP. If CAB PrEP is permanently discontinued, the PSP will not remain in the study. See the SoA (ANNEX 1 and ANNEX 2) and for data to be collected at the time of discontinuation of CAB PrEP. All study and CAB PrEP discontinuations will be captured in the eCRF.

A PSP may have to discontinue CAB PrEP due to moderate to severe (as clinically determined by the PrEP provider) COVID-19 infection (suspect, probable, or confirmed using the most recent version of the World Health Organization (WHO) case definition (WHO 2020).

All study and CAB PrEP discontinuations will be recorded in the eCRF.

9.2. Temporary Discontinuation

If CAB PrEP is temporarily discontinued for any reason, then the PrEP provider will: 1) record temporary discontinuations and restart information in the eCRF; and 2) will be responsible for clinical decision and management regarding the use of another recommended PrEP regimen to maintain PrEP coverage. If the PSP does not restart CAB PrEP, ie, if CAB PrEP is permanently discontinued, then such PSP will no longer be eligible to continue the study.

9.3. Participant Discontinuation / Withdrawal from the Study

A PSP may discontinue CAB PrEP and withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the PrEP providers for safety (i.e., AE, SAE), behavioral, or compliance reasons (i.e., protocol deviation), administration of contraindicated medicines, or their own decision (consent withdrawal).

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. The SoA includes the data to be collected at the time of study discontinuation, i.e. for safety monitoring purposes.

If the PSP withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

An SSP may withdraw from the study at any time at their own request. If the SSP is changing roles, the individual assuming the role will be enrolled in the study as an SSP. If the no one else assumes the role and is not subsequently enrolled as an SSP, reasons for the SSPs withdrawal will be ascertained.

9.4. Lost to Follow-up

A PSP will be considered lost to follow-up if they fail to return for one or more scheduled visits and are unable to be contacted by the PrEP provider.

The following actions must be taken if a PSP fails to return to the site for a required study visit:

- The PrEP provider must attempt to contact the PSP and reschedule the missed visit as soon as possible and counsel the PSP on the importance of maintaining the assigned visit schedule and ascertain whether or not the PSP wishes to and/or should continue on study and receiving injections at the site.
- Before a PSP is deemed lost to follow up, the PrEP provider must make every effort to regain contact with the PSP. These contact attempts should be documented in the PSP's medical record.
- When possible, a maximum of three telephone calls and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods will have been done before a participant has been considered 'unreachable'. Should the PSP continue to be unreachable after these efforts are extended, they will be

considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

- A SSP will be considered lost to follow-up only if that SSP role in the clinic is eliminated. Additionally, a SSP who leaves their role will be replaced with the SSP who assumes the role to complete subsequent assessments.

10. SPECIFIC ADVERSE EVENTS, SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) or serious adverse events (SAEs) can be found in ANNEX 4. For adverse events (AEs), only those that are considered related to CAB PrEP, or that caused the PSPs to discontinue the study are required to be reported in the eCRF (See Section 10.1).

The definitions of unsolicited and solicited adverse events can be found in ANNEX 4.

The definitions of device-related safety events, adverse device effects (ADEs) and serious adverse device effects (SADEs), can be found in ANNEX 5. Device deficiencies are covered in Section 10.4.5.

AEs will be reported by the PSP (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The PrEP Provider and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the PSP to discontinue CAB PrEP (see Section 10.1).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in ANNEX 4.

Please refer to ANNEX 6 for study management information during the COVID-19 pandemic.

10.1. Specific Adverse Events to be Documented in this Study

Please refer to the USPIs for CAB tablets for PrEP and APRETUDE for additional safety information

Adverse events that occur during the trial should be evaluated by the SSP and graded according to the Division of AIDS (DAIDS) toxicity scales Version 2.1 July 2017.

AEs and SAEs that are required to be recorded as defined in the eCRF include:

- AEs/ADRs considered related to CAB PrEP
    - Note: Non-serious injection site reactions do not have to be reported to Vendor.
- AEs/Adverse drug reactions (ADRs) reported at the Baseline visit that are considered related to CAB tablets for PrEP (if used as optional oral lead-in)
- All AEs, including ISRs, whether considered related or not, that cause the participant to discontinue CAB PrEP
- All SAEs whether related to CAB PrEP or not

The PrEP provider are obliged to collect and report from the time of informed consent to PSP's completion of study or study withdrawal, all non-serious ADRs, (excluding non-serious ISRs), AEs leading to withdrawal and all SAEs listed above, to the CRO.

As ISRs have been well characterised throughout the clinical development program for CAB PrEP and are considered common adverse drug reactions for CAB PrEP, therefore only serious ISRs and ISRs leading to discontinuation are required to be reported to Vendor as described in above.

Non serious AEs that are considered not related to CAB PrEP by the SSP or do not lead to withdrawal, should be documented in the source documents but will not be documented in the eCRF, as this information has been extensively collected in PrEP clinical trials, no further information is needed to characterize these events.

10.2. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the informed consent form until the until the PSP completes or withdraws from the study, at the timepoints specified in the SoA (ANNEX 1 & ANNEX 2).
- AEs that begin during the oral lead-in and are considered by the PrEP Provider to be related to CAB PrEP will be recorded as a CAB PrEP related AE after obtaining the informed consent.
- All other events that begin before the administration of CAB PrEP but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions section of the case report form (CRF) not as AEs.
- All non-serious ADRs will be collected from Day 1 until the follow-up visit at the time points specified in the SoA (ANNEX 1 & ANNEX 2).
- AEs that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in ANNEX 4. The PrEP Provider will submit any updated SAE data to the sponsor within 24 hours of it being available.
- PrEP Providers are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the PrEP Provider learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the PrEP Provider must promptly notify the sponsor.

10.2.1. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

10.2.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the PrEP provider is required to proactively follow each PSP at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 9.4). Further information on follow-up procedures is given in the SRM.

10.2.3. Regulatory Reporting Requirements for SAEs

The definition serious adverse events (SAEs) can be found in Section 12.4.2ANNEX 4. Prompt notification by the site to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of CAB PrEP are met. All SAEs need to be reported within 24 hours of documentation sent by an automated, electronic safety alert within the CRF.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of CAB PrEP. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB) and PrEP providers with participants in this study.

The site which receives a safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the required study documents and will notify the IRB, if appropriate according to local requirements.

Safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to participating PrEP providers as necessary.

10.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

10.3.1. Clinical safety laboratory assessments

Laboratory assessments for this study will be performed at local laboratories. The PrEP provider must review the laboratory reports and should follow local or CDC PrEP management guidelines for laboratory assessments during PrEP.

- The PrEP provider will determine if any laboratory tests have values considered clinically significant and will be responsible for the participant clinical management. The laboratory reports must be filed with the source documents.

Testing for HIV-1 RNA and liver chemistries (if performed at the discretion of the PrEP provider) will be analyzed by the local labs (refer to SRM for further details).

Additional tests may be performed at any time during the study as determined necessary by the PrEP provider and in accordance with the current CDC PrEP guidelines.

10.3.2. Liver Chemistry Monitoring

The management of liver safety and the decision whether to discontinue CAB PrEP in the presence of abnormal liver tests should be at the discretion of the PrEP provider and in line with the prescribing information for CAB tablet for PrEP and APRETUDE with PrEP CDC clinical management guidelines.

In cases where the PrEP provider suspects a PSP has an event of hepatotoxicity, the liver eCRF forms will also need to be completed, in addition to any corresponding AE or SAE form. The additional forms will gather further details of the liver event and should be completed in a timely manner.

10.4. Adverse Events (AEs), Pregnancy Exposure and Incident Reporting

All PSP clinical safety data will be collected as outlined in the eCRF. No clinical safety data will be collected for SSPs.

10.4.1. Definition of adverse events

An AE is any untoward medical occurrence in a PSP, temporally associated with the use of CAB PrEP, whether or not considered related to a medicinal product.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of CAB PrEP.

AEs will be reported by the PSP (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative [LAR]) and be collected and stored in the participants source documentation.

The PrEP provider should assess all reported AEs and SAEs for follow-up medical management and to determine relatedness to CAB PrEP. When a causality relationship is determined by the PrEP provider to be related to CAB PrEP, this must be recorded as a treatment related AE or SAE.

Adverse events that occur during the trial should be evaluated by the SSP and graded according to the DAIDS toxicity scales Version 2.1 July 2017. Further details of the definitions of adverse events (AE) or serious adverse events (SAEs) can be found in ANNEX 4.

10.4.1.1. Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a noxious and unintended response to a medication related to any doses where there is at least a reasonable possibility, or the relationship cannot be ruled out, that it is related to CAB PrEP.

10.4.1.2. Injection Site Reactions

Injection site reactions (ISRs) are considered drug related as they are related to the administration of CAB PrEP. ISRs may include redness, itching, pain or swelling or discomfort at the site of the reaction.

As ISRs have been well characterized throughout the clinical development program for CAB PrEP and are considered common adverse drug reactions for CAB PrEP, therefore

only serious ISRs and ISRs leading to discontinuation are required to be reported to Vendor as described in ANNEX 4.

10.4.2. Reporting of AEs and timelines

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. All AEs listed in 10.1 will require reporting within 3 calendar days.

> If the eCRF is unavailable at the time of notification of these events, a paper form will need to be completed and sent to the sponsor or designee.

Prompt notification by the site the sponsor or designee of these events is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of CAB PrEP are met.

10.4.3. Pregnancy

Pregnancy testing will be managed by the PrEP provider and in accordance with CDC PrEP guidelines.

If a pregnancy is reported, the site will record pregnancy information on the appropriate form and submit it to Sponsor or designee within 24 hours of learning of the pregnancy. Pregnancies will also be directly reported to the Antiretroviral Pregnancy Registry (APR) by the PrEP provider. The procedure for reporting is outlined in the SRM.

The PrEP provider will be given necessary "pregnancy notification" and "pregnancy follow up" forms and supported by clinical monitor and/or Sponsor medical team in complying with regular pregnancy reporting procedures. Pregnancies will also be reported to the APR by the Sponsor. The PrEP Provider must not report to APR, to avoid duplication.

All pregnancies must be followed up to until outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE (elective terminations for nonmedical reasons should be reported as non-serious AEs). Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Any SAE occurring in association with a pregnancy brought to the site's attention after the PSP has completed the study and considered by the PrEP provider as possibly linked to CAB PrEP exposure, must be promptly reported to Sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the PrEP provider will be reported to the Sponsor (refer to the SRM for details). While the PrEP provider is not obligated to actively seek this information in former PSPs, they may learn of an SAE through spontaneous reporting.

The APR is jointly sponsored by manufacturers or licensees of ARV products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

Prior to continuation of CAB PrEP following pregnancy, the following must occur:

- PrEP provider confirms CAB PrEP can be continued and this documentation is stored in the PSP's source documents.

- The site agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring at birth.

10.4.4. Cardiovascular and Death Events

All deaths will be reported as SAEs. In addition, all deaths will be required to have the eCRF death forms completed by the site. These sections include questions regarding the death (including sudden cardiac death and non-cardiovascular death).

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up eCRF reports regarding death must be completed within one week of when the death is reported.

For any cardiovascular events detailed in ANNEX 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These mandatory sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death. They will only be used as required per the nature of the SAE.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

10.4.5. Medical Device Deficiencies

To fulfil regulatory reporting obligations worldwide, the SSP is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in ANNEX 5

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in ANNEX 4 of the protocol.

10.4.5.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be reported during all periods of the study in which the medical device is used.

- If the SSP learns of any device deficiency at any time after a participant has been discharged from the study, and such a device deficiency is considered reasonably related to a medical device provided for the study, the PrEP Provider will promptly notify the sponsor.

10.4.5.2. Prompt Reporting of Medical Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the SSP determines that the event meets the protocol definition of a device deficiency.
- The method of reporting of Medical device deficiencies is outlined in ANNEX 5.
- The sponsor will be the contact for the receipt of device deficiency reports.

10.4.5.3. Regulatory Reporting Requirements for Device Deficiencies

- The SSP will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The SSP, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

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12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1. ANNEX 1: Schedule of Activities – DIRECT TO inject (DTI)

Procedure[1]	**Screening/ Eligibility/ Enrolment**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1[3]	**M2**	**M3**	**M4**[10]	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
	Up to 90 days	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		

1. The timing and number of planned study assessments, specifically interviews with SSPs and PSPs, may be altered during the study based on newly available data. Brief interviews may be held at other times based on learnings during implementation.
2. Benefits verification should be performed at the start of the screening period, which may be extended up to 90 days to allow for this confirmation. Screening/eligibility procedures (excluding informed consent) should not be performed prior to receiving this confirmation. Additionally, in line with the USPI, all patient participants require proof of a negative HIV test, dated within the 7 days prior to PrEP initiation, regardless of any prior negative test results. During screening/ enrollment, the following will be completed for PSPs: 1) Informed consent form (ICF), 2) Benefits verification, as required, 3) Confirm Inclusion and Exclusion criteria, 4) Demography 5) Medical History, including history of hepatitis C virus infection, and current medical conditions 6) required labs per clinical local standard of care. Screening/ enrollment can occur on the same date as the first APRETUDE injection as long as a negative HIV test is documented within 7 days prior to initiation of APRETUDE. Refer to Section 4.3.1 for details on re-screening for PSPs who fail screening.
3. Dose 1(D1) is defined as the date of first APRETUDE injection. The following sequence of events must be followed for participants at this visit: 1) complete surveys and assessments prior to or at the visit, and 2) Receive first IM injections at the visit.
4. The treatment period is based on 12 calendar months. The last APRETUDE injection is to occur at the last study visit.
5. E.D = early discontinuation/ withdrawal: This visit should only be conducted if the participant discontinues from the study prior to completing the Study at Month 12, and the discontinuation/withdrawal reason should be recorded. For SSPs, this visit will only occur if the SSP withdraws and remains in the role for which they were enrolled, and no replacement is possible.

Procedure[1]	**Screening/ Eligibility/ Enrolment**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1[3]	**M2**	**M3**	**M4**[10]	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
	Up to 90 days	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Clinical and Other Assessments															
Informed consent	X														Written informed consent must be obtained from each potentially eligible participant by site personnel prior to the initiation of any M1 procedures as outlined in this protocol.
Inclusion and exclusion criteria	X														Inclusion/exclusion criteria will be fully implemented during screening.
Benefits verification, as needed[2]	X														
Demography	X														

Procedure[1]	**Screening/ Eligibility/ Enrolment**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1[3]	**M2**	**M3**	**M4**[10]	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
	Up to 90 days	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Laboratory assessments	X Needed at BL, M4 and end of study, can be just HIV test and STI testing.	Lab assessments, including HIV testing and STI clinical diagnoses (defined for this study as syphilis (any stage), gonorrhea, chlamydia, or trichomonas) at Screening and during study duration should be performed using local laboratories and should be in accordance with the CDC PrEP clinical management guidelines and the USPI or per clinical local standard of care. All lab reports must be stored in the participants source documentation at the clinical sites with only the protocol-specified test results to be reported in the eCRF*. For PSPs with incident HIV-1 infections, all available HIV-1 test results (HIV Test Result (positive, negative and indeterminate), HIV Test Type (HIV-1 antibody/antigen test and HIV-1 RNA) conducted by the site as standard of care and, if applicable and available, the start date of ART and ART regimen (by category) used will be reported in the eCRF.												X	*All performed HIV test results (regardless of result, including positive, negative, or indeterminate) and HIV test type will be reported in the eCRF. For other laboratory tests, only abnormal laboratory results associated with AEs leading to study discontinuation, as well as any clinical diagnosis (made by PrEP provider) of STIs will be reported in the eCRF.
Study Treatment: Participants who are started on oral CAB PrEP as optional oral lead in will receive their first dose of oral CAB on Day 1. Participants who are started on APRETUDE injections (direct to inject) will receive their first dose of APRETUDE injection on Day 1. **All injections will be administered according to the Cabotegravir LA PrEP USPI.**															
Cabotegravir LA PrEP IM Initiation injections		X													

Procedure[1]	**Screening/ Eligibility/ Enrolment**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1[3]	**M2**	**M3**	**M4**[10]	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
	Up to 90 days	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Cabotegravir LA PrEP IM Maintenance injections			X		X		X		X		X		X		IM dosing is expected to occur on the same date of the month as determined by Dose 1 - Treatment Target Date. Dosing window is (+ or -) a 7-day window as per the USPI.
Concomitant medication review	X	←==========→												X	Record in CRF if; contraindicated medications, concomitant medications with a potential for a DDI per the CAB tablet for PrEP or APRETUDE USPI.
Medical history	X														
Adverse Event (AE) Review		X	←==========→											X	Only drug related AEs and AEs leading to CAB Prep discontinuation will be collected in the eCRF.

Procedure[1]	**Screening/ Eligibility/ Enrolment[2]**	**Treatment Period[4]** Month(M)/Dose(D)												**E.D.[5]**	**Notes**
		M1[3]	**M2**	**M3**	**M4[10]**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
	Up to 90 days	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Serious AEs (SAEs)		X	←==========										==========→	X	All SAEs regardless of relatedness will be collected in the eCRF.
Pregnancy	X	X	←==========										==========→	X	Ask WOCBP at each visit if they are pregnant and ask for the date of their LMP.
Surveys and Interviews: Surveys and Interviews should be completed before receiving APRETUDE IM injections															
Patient Study Participants 6 - Participants baseline questionnaires and interviews should be completed within three weeks prior to or on their D1 visit and before receiving the first APRETUDE injection. Participants M4 questionnaires should be completed within 2 weeks before or 2 weeks following study visit. Participants M12 questionnaires and interviews should be completed within 2 weeks before or 2 weeks following study visit. 7 - Approximately three participants per site will be interviewed; sites with larger volume of participants might have more interviews. Participants will be purposely sampled for interviews based on demographic characteristics, such as, prior PrEP use (see 5.1.4.1). All additional study visits, including those where surveys and/or interviews are administered at M4 and M12, will be anchored off of each participants DOSE 1 visit, so it reflects months in study, regardless of what dose they are on and regardless of whether they have missed any injections and received oral PrEP.														
Sexual Health Assessments	X														
PSP Surveys[6]		X			X								X	X	To be completed prior to injection

Procedure[1]	**Screening/ Eligibility/ Enrolment**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1[3]	**M2**	**M3**	**M4**[10]	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
	Up to 90 days	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Participant Interviews[6,7]		X											X	X	Interviews will be completed on a subset of PSPs.[7]
Staff Study Participants: Baseline surveys should be completed prior to the first participant being enrolled 8 - Baseline IS assessment is defined as the first assessment taken prior to administering the first IM injection to the first participant at each site. Baseline questionnaires should be completed by all SSPs within 1-2 weeks of their completed site initiation. 9 - SSP M4 and M12 questionnaires and/or interviews can be completed within 3 weeks of study visits. 10 - For sites with both OLI and DTI participants, M4/M5 visit will be defined when at least 1 participant, at their respective site, has completed their M4(DTI)/M5(OLI) study visit (Dose 3 visit), respectively, whichever comes first. M12/M13 visit will be defined after at least 1 participant, at their respective site, has completed their M12(DTI)/M13(OLI) study visit (Dose 7 visit), whichever comes first. If the site only has DTI patients, the visits will be defined at M4 and M12, respectively. If a site has only OLI patients, the SSP assessment follows the OLI SOA in ANNEX 2. 11 - Implementation monitoring and aggregate clinic PrEP-related data collection can start prior to participant enrolment.															
SSP Surveys[9]	X[8]				X								X		At least 1 participant must include an SSP who prescribes APRETUDE.
SSP Interviews[9]					X								X		
Implementation Monitoring[11]		X	X	X	X	X	X	X	X	X	X	X	X		
Site level PrEP Information Questionnaire	X				X				X				X		Aggregate clinic PrEP-related data. Selected SSPs in the SI, EI, and ECI arms will be asked to complete.

12.2. ANNEX 2: Schedule of Activities – Optional oral lead in

Procedure[1]	Screening/ Eligibility/ Enrolment	Treatment Period[3] Months (M) & Dose (D)												E.D.[5]	Notes
	Up to 90 days	M1 (at least 28 days)	M2	M3	M4	M5[10]	M6	M7	M8	M9	M10	M11	M12	M13	
		OLI	D1 visit	D2 visit		D3 visit		D4 visit		D5 visit		D6 visit		D7 visit	

1. The timing and number of planned study assessments, specifically interviews with SSPs and PSPs, may be altered during the study based on newly available data. Brief interviews may be held at other times based on learnings during implementation.
2. Benefits verification should be performed at the start of the screening period, which may be extended up to 90 days to allow for this confirmation. Screening/eligibility procedures (except informed consent) should not be performed prior to receiving this confirmation. Additionally, in line with the USPI, all patient participants require proof of a negative HIV test, dated within the 7 days prior to PrEP initiation, regardless of any prior negative test results. During screening/enrollment, the following will be completed for PSPs: 1) Informed consent form (ICF), 2) Benefits verification, as required, 3) Confirm Inclusion and Exclusion criteria, 4) Demography 5) Medical History, including history of hepatitis C virus infection, and current medical conditions 6) required labs per clinical local standard of care. Screening/enrollment can occur on the same date as the start of OLI as long as a negative HIV test is documented within 7 days prior to initiation of CAB PrEP. Refer to Section 4.3.1 for details on re-screening for PSPs who fail screening.
3. Dose 1 (D1) is defined as the date of first APRETUDE injections. The following sequence of events must be followed for participants at the D1 visit: 1) completion of surveys and assessments prior to or at the visit, and 2) Receipt of first IM injections at the visit. The last APRETUDE injection is to occur at the last study visit
4. The treatment period is based on 12 calendar months. The last APRETUDE injection is to occur at the last study visit.
5. E.D = early discontinuation/ withdrawal: This visit should only be conducted if the participant discontinues from the study prior to completing the Study at Month 13, and the discontinuation/withdrawal reason should be recorded.

Procedure[1]	**Screening/ Eligibility/ Enrolment**	**Treatment Period[3]** Months (M) & Dose (D)													**E.D.[5]**	**Notes**
	Up to 90 days	**M1 (at least 28 days)**	**M2**	**M3**	**M4**	**M5[10]**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
		OLI	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Clinical and Other Assessments																
Informed consent	X															Written informed consent must be obtained from each potentially eligible PSP by site personnel prior to the initiation of any M1 procedures as outlined in this protocol.
Inclusion and exclusion criteria	X															Inclusion/exclusion criteria will be assessed during screening.
Benefits verification, as needed[2]	X															
Demography	X															

Procedure[1]	**Screening/ Eligibility/ Enrolment**	**Treatment Period**[3] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
	Up to 90 days	**M1 (at least 28 days)**	**M2**	**M3**	**M4**	**M5**[10]	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
		OLI	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Laboratory assessments	X Needed at BL, M5 and end of study, can be just HIV test and STI testing, but shouldn't be completely non-prescriptive	Lab assessments, including HIV testing and STI clinical diagnoses (defined for this study as syphilis (any stage), gonorrhea, chlamydia, or trichomonas) at screening and during PrEP should be performed using local laboratories and in accordance with the CDC PrEP clinical management guidelines and the USPI or per clinical local standard of care. All lab reports must be stored in the participants source documentation at the clinical sites with only the protocol-specified test results to be reported in the eCRF*. For PSPs with incident HIV-1 infections, all available HIV-1 test results (HIV Test Result (positive, negative and indeterminate), HIV Test Type (HIV-1 Antibody/Antigen test and HIV-1 RNA) conducted by the site as standard of care and, if applicable and available, the start date of ART and ART regimen (by category) used will be reported in the eCRF.												X	*All performed HIV test results (negative or positive) and HIV test type will be reported in the eCRF. For other laboratory tests, only abnormal laboratory results associated with AEs leading to study discontinuation, as well as any clinical diagnosis (made by PrEP provider) of STIs will be reported in the eCRF.
Study Treatment: Participants who are started on oral Cabotegravir PrEP as optional oral lead in will receive their first dose of oral CAB on Day 1. Participants who are started on APRETUDE injections (direct to inject) will receive their first dose of APRETUDE injection on Day 1. **All injections will be administered according to the APRETUDE USPI.**																

Procedure[1]	**Screening/ Eligibility/ Enrolment**	**Treatment Period**[3] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
	Up to 90 days	**M1 (at least 28 days)**	**M2**	**M3**	**M4**	**M5**[10]	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
		OLI	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
CAB tablets for PrEP		X														
APRETUDE IM Initiation injections			X													For PSPs receiving optional OLI, 1st injection occurs following completion of OLI and the final oral doses of OLI should be taken on the same day when injections with APRETUDE are started.

Procedure[1]	**Screening/ Eligibility/ Enrolment**	**Treatment Period**[3] Months (M) & Dose (D)												**E.D.**[5]	**Notes**
	Up to 90 days	**M1 (at least 28 days)**	**M2**	**M3**	**M4**	**M5**[10]	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	
		OLI	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**	
APRETUDE IM Maintenance injections				X		X		X		X		X		X	IM dosing is expected to occur on the same date of the month as determined by Dose 1 - Treatment Target Date. Dosing window is (+ or -) a 7-day window as per the USPI.
Concomitant medication review	X	←==========→												X	Record in CRF if; contraindicated medications, concomitant medications with a potential for a drug-drug interaction (DDI) per the CAB tablet for PrEP or APRETUDE USPI
Medical History	X														

Procedure[1]	**Screening/ Eligibility/ Enrolment**	**Treatment Period**[3] Months (M) & Dose (D)												**E.D.**[5]	**Notes**
	Up to 90 days	**M1 (at least 28 days)**	**M2**	**M3**	**M4**	**M5**[10]	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	
		OLI	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**	
Adverse Event (AE) Review		X	←==========											→| X	Only drug related AEs and AEs leading to CAB Prep discontinuation will be collected in the eCRF.
Serious AEs (SAEs)		X	←==========											→| X	all SAEs regardless of relatedness will be collected in the eCRF.
Pregnancy	X	←==========												→| X	Ask WOCBP at each visit if they are pregnant and ask for the date of their LMP.
Surveys and Interviews: Surveys and Interviews should be completed before receiving APRETUDE IM injections															

Procedure[1]	Screening/ Eligibility/ Enrolment	Treatment Period[3] Months (M) & Dose (D)													E.D.[5]	Notes
	Up to 90 days	M1 (at least 28 days)	M2	M3	M4	M5[10]	M6	M7	M8	M9	M10	M11	M12	M13		
		OLI	D1 visit	D2 visit		D3 visit		D4 visit		D5 visit		D6 visit		D7 visit		
Patient Study Participants 6 - Participants baseline questionnaires and interviews should be completed within three weeks prior to or on their D1(M2) visit and before receiving the first APRETUDE injection. Participants M5 questionnaires should be completed within 2 weeks before or 2 weeks following study visit. Participants M12 questionnaires and interviews should be completed within 2 weeks before or 2 weeks following study visit. 7 - Approximately three participants per site will be interviewed; sites with larger volume of participants might have more interviews. Participants will be purposely sampled for interviews based on demographic characteristics, such as, prior PrEP use (see 5.1.4.1). All study visits, including those where surveys and/or interviews are administered at M5 and M13, will be anchored off of each participant's D1 visit, regardless of what dose they are on and regardless of whether they have missed any injections and received oral PrEP																
Sexual Health Assessment	X															
PSP Surveys[6]			X			X								X	X	To be completed in Month 2 prior to the injection within Month 2.
Participant Interviews[6, 7]			X											X	X	Interviews will be completed on a subset of PSPs.[7]

Procedure[1]	Screening/ Eligibility/ Enrolment	Treatment Period[3] Months (M) & Dose (D)												E.D.[5]	Notes
	Up to 90 days	M1 (at least 28 days)	M2	M3	M4	M5[10]	M6	M7	M8	M9	M10	M11	M12	M13	
		OLI	D1 visit	D2 visit		D3 visit		D4 visit		D5 visit		D6 visit		D7 visit	
Staff Study Participants: Baseline surveys should be completed prior to the first participant is enrolled 8 - Baseline IS assessment is defined as the first assessment taken prior to administering the first IM injection to the first participant at each site. Baseline questionnaires should be completed by all SSPs within 1-2 weeks of their completed site initiation. 9 - SSP M5 and M13 questionnaires and/or interviews can be completed within 3 weeks of study visits. 10 - For sites with both OLI and DTI participants, M4/M5 visit will be defined when at least 1 participant, at their respective site, has completed their M4(DTI)/M5(OLI) study visit (Dose 3 visit), respectively, whichever comes first. M12/M13 visit will be defined after at least 1 participant, at their respective site, has completed their M12(DTI)/M13(OLI) study visit (Dose 7 visit), whichever comes first. If a site has only OLI patients, the visits will be defined as M5 and M13. If the site only has DTI patients, SSP assessments follow the DTI SOA in ANNEX 1. 11 - Implementation monitoring and aggregate clinic PrEP-related data collection can start prior to participant enrolment.															
SSP Surveys[9]	X					X								X		At least 1 consistent SSP knowledgeable of implementation to participate.
Staff Interviews[9]						X								X		
Implementation Monitoring [11]			X	X	X	X	X	X	X	X	X	X	X	X		

Procedure[1]	**Screening/ Eligibility/ Enrolment**	**Treatment Period**[3] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
	Up to 90 days	**M1 (at least 28 days)**	**M2**	**M3**	**M4**	**M5**[10]	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
		OLI	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Site level PrEP Information Questionnaire	X				X				X				X			Aggregate clinic PrEP-related data. Selected SSPs in the SI, EI, and ECI arms will be asked to complete.

12.3. ANNEX 3: List of Stand-Alone Documents

Study Reference Manual (SRM)

12.4. ANNEX 4: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

12.4.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited using a PSP diary and that is communicated by a PSP/ PSP's parent(s)/ LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The PSP/ PSP's parent(s)/ LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of PSP/ PSP's parent(s)/ LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified SSPs and documented in the PSP's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the PSP/ PSP's parent(s)/ LAR(s) will be collected during an interview with the PSP/ PSP's parent(s)/ LAR(s) and by review of available medical records at the next visit. • Solicited AEs are predefined at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the PrEP Provider (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the PrEP Provider to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the PrEP Provider in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. ○ Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias,

convulsions, or development of intervention dependency or intervention abuse.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
PrEP Provider will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.4.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the PrEP Provider to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The PrEP Provider will then record all relevant AE/SAE information. • It is **not** acceptable for the PrEP Provider to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The PrEP Provider will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
• The PrEP Provider will assess intensity for each AE and SAE reported during the study according to the DAIDS toxicity scales Version 2.1 July 2017.

Assessment of Causality

- The PrEP Provider is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The PrEP Provider will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The PrEP Provider will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the PrEP Provider **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the PrEP Provider has minimal information to include in the initial report to GSK. However, **it is very important that the PrEP Provider always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The PrEP Provider may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The PrEP Provider is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the PrEP Provider will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The PrEP Provider will submit any updated SAE data to GSK within 24 hours of receipt of the information.

12.4.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next Section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor and safety team. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the PrEP Provider to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for paper SAE reporting can be found in the SRM.

12.5. ANNEX 5: Medical device reporting Definition of Medical Device AE and ADE

12.5.1. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

12.5.2. Reporting of Medical Device Deficiencies

Reporting to GSK
• Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com. • If the device incident is linked to an SAE, please email gsk-rd.complaints@gsk.com, within 24 hours. The associated SAE form should also be reported to Sponsor.

12.6. ANNEX 6: COVID-19 Pandemic and Clinical Trial Continuity

This appendix outlines the measures which are approved for implementation within this clinical trial, to protect patient safety and to ensure the integrity of the clinical trial, as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Independent Review Boards/Independent Ethics Committees and National Competent Authorities, as necessary.

This appendix **does not** apply to participant management issues that are unrelated to a specific, and documented, impact from COVID-19.

12.6.1. Changes to Study Visits and Study Procedures

- Where site staff resource is constrained due to COVID-19, IM dosing visits may proceed with limited or no other protocol-defined assessments (e.g. lab tests, surveys, etc.). If lab tests will be missed for more than one consecutive visit, the medical monitor may be contacted, to provide guidance for safety monitoring.
- When on-site visits are reduced, it is important that the investigator continue collecting relevant clinical information, including adverse events, from the participant through alternative means, e.g. by telephone contact.
- There may be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.
- There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, to protect a study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations.

12.6.2. Changes to Informed Consent

Informed consent should continue per normal procedure and as described in the main body of the protocol, to the extent possible. However, there may be circumstances where if written re-consent of participants is needed, and a physical signature on site is not possible. In these cases, alternative ways of obtaining such re-consent should be considered, such as the participant sending a picture of his/her written consent to the investigator, or the investigator contacting the participant by telephone or video call and obtaining verbal consent, supplemented with email confirmation.

Any updated informed consent form or other participant-facing materials should be provided to participants before re-consent is obtained. Any consent obtained in an alternative way should be documented in source records and confirmed by way of normal consent procedure at the earliest opportunity when participants attend their next on-site study visit.

Any alternative informed consent procedure must be undertaken only after site IRB/Ethics Committee agreement and approval.

12.6.3. COVID-19 Specific Data Capture

12.6.3.1. Capturing COVID-19 Specific Protocol Deviations

Please refer to your study procedure manual for specific details on capturing protocol deviations as a result of COVID-19.

12.6.3.2. Capturing COVID-19 Specific AEs and SAEs

It is important for the study team to describe COVID-19 related adverse events/serious adverse and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines.

2. When an in-person clinic visit is not possible, please conduct a remote telehealth visit to assess for, and document any AEs/SAEs.

3. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released March 20, 2020, represents a time point for standardized collection. We recognize definitions are likely to continue to evolve. When reporting both serious and non- serious adverse events (related to COVID-19 infection, investigators should use the following Verbatim terms:
    a) Suspected COVID-19 infection; or
    b) Probable COVID-19 infection; or
    c) Confirmed COVID-19 infection

4. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation.

WHO Case Definition - March 20, 2020 Version (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)):

Suspected case:

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or

residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

B. A patient with any acute respiratory illness AND in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive (Inconclusive being the result of the test reported by the laboratory).

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Covid-19 Contact:

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR
4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

12.7. ANNEX 7: Regulatory, Ethical and Study Oversight Considerations

12.7.1. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

12.7.2. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ViiV Healthcare/ GSK site or other mutually agreeable location.
- ViiV Healthcare/ GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the PSPs and SSPs, as appropriate.
- Under the framework of the SHARE initiative, ViiV Healthcare/ GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by PSPs and SSPs are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with ViiV Healthcare/ GSK Policy.
- ViiV Healthcare/ GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by PSPs and SSPs, are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

12.7.3. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs or Electronic Data Capture System (EDC) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs and EDC will be provided in the investigator site file.
- Quality tolerance limits (QTLs) will be pre-defined in a QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.7.4. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.7.5. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first centre initiated (first site open) and will be the study start date.

Study/Site Termination

ViiV Healthcare/ GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of ViiV Healthcare/ GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

12.7.6. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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