Information Type: ViiV Healthcare Interventional Study Protocol

Title:	A Phase 4, randomized, open-label, two-arm study evaluating implementation strategies for the delivery of Cabotegravir in low and high-volume pre-exposure prophylaxis (PrEP) sites in the U.S. for HIV uninfected MSM and transgender men ≥ 18

Protocol Number: 217710/ Amendment 2

Compound Number: GSK1265744, Cabotegravir

Brief Title: A study evaluating implementation strategies for the delivery of Cabotegravir in low and high-volume PrEP site in the U.S.

Development Phase Phase 4

Acronym: PILLAR - PrEP Implementation Study for Cabotegravir Long Acting for Men in the Real World

Sponsor Name and Legal Registered Address (excluding US):

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

US IND Sponsor Legal Registered Address:

ViiV Healthcare Company
410 Blackwell Street
Durham, NC 27701, USA
Telephone: +1 919 438 2100

In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Senior Vice President, Head of Research & Development.

This study is sponsored by ViiV Healthcare. GSK, Syneos Health and Evidera are supporting ViiV Healthcare in the conduct of this study.

Marketing Authorisation Holder:

ViiV Healthcare Company

Regulatory Agency Identifying Number(s): IND: 109,678

Medical Monitor Name and Contact Information will be provided separately

Sponsor Signatory

Dr Annemiek de Ruiter
VP & Head of Global Medical Sciences
ViiV Global Medical

Approval Date: 13 Apr 2023

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 AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment [2]	*13 Apr 2023*	*TMF-15754477*
Amendment [1]	*18-February-2022*	*TMF-14446771*
Original Protocol (00)	*26-October-2021*	*TMF-14064431*

Amendment [2] 13 Apr 2023

Overall Rationale for the Amendment: The protocol has been updated to simplify the language used to describe primary, secondary and tertiary endpoints. The information removed from the endpoint descriptions was duplicated in the statistical analysis section and is more appropriate to be described there. Updates have also been made to the diversity targets of the study. Various clarifications to the schedules of assessments have been made based on site feedback and ViiV/GSK updated mandatory text has been incorporated where appropriate. All changes are considered non-substantial.

Minor editorial changes for accuracy, clarity, formatting and consistency have been made throughout the document and are not included in the description(s) below

Bold: Newly added text

Section	Current text	Proposed text	Rationale for change
Title	ViiV Healthcare Company Five Moore Drive P.O. 13398 Research Triangle Park, NC 27709-3398, USA **Sponsor Signatory** Dr Sherene Shakib Min, MD, MPH VP, Head of Clinical Development ViiV Research & Development	ViiV Healthcare Company ~~Five Moore Drive~~ ~~P.O. 13398~~ ~~Research Triangle Park, NC 27709-3398, USA~~ **410 Blackwell Street** **Durham, NC 27701, USA** Telephone: +1 919 438 2100 **In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Senior Vice President, Head of Research & Development.** **This study is sponsored by ViiV Healthcare. GSK, Syneos Health and Evidera are supporting ViiV Healthcare in the conduct of this study.** **Sponsor Signatory** **Dr Annemiek de Ruiter** **VP & Head of Global Medical Sciences** **ViiV Global Medical**	Updated Sponsor address due to recent office relocation. Added mandatory ViiV protocol language that was omitted from previous version in error. Changed Sponsor Signatory to reflect recent internal responsibility changes.

2 – Objectives and Endpoints	• Objectives	• Endpoints	• Objectives	• Endpoints	Multiple endpoints have been simplified to remove information that was duplicated in the statistical analysis section of the protocol. One new tertiary endpoint has been added.
	• Primary		• Primary		
	• To evaluate feasibility of dynamic implementation (DI) compared to routine implementation (RI) for APRETUDE administration.	• Staff study participants' (SSPs) mean Feasibility of Intervention Measure (FIM) score at M13[1] by study arm, and clinic characteristics (e.g., volume).	• To evaluate feasibility of dynamic implementation (DI) compared to routine implementation (RI) for APRETUDE administration.	• Staff study participants' (SSPs) mean Feasibility of Intervention Measure (FIM) score at M13[1] ~~by study arm, and clinic characteristics (e.g., volume)~~.	
	• Secondary		• Secondary		
	• To evaluate change in feasibility of RI and DI for APRETUDE administration	• Change from baseline in SSPs' FIM score at M5 and M13 by study arm and clinic characteristics. • SSPs perceptions of facilitators and barriers to RI and DI and overall implementation of PrEP into routine	• To evaluate change in feasibility of RI and DI for APRETUDE administration	• Change from baseline in SSPs' FIM score at M5 and M13 ~~by study arm and clinic characteristics~~. • SSPs perceptions of facilitators and barriers to RI and DI and overall implementation of PrEP into routine	

		care assessed by semi-structured qualitative interviews (SSIs), implementation science questionnaire (ISQ), FRAME-IS, implementation monitoring calls (IMC)and facilitation calls through M13.		care assessed ~~by semi-structured qualitative interviews (SSIs), implementation science questionnaire (ISQ), FRAME-IS, implementation monitoring calls (IMC)and facilitation calls~~ through M13.	
	• To evaluate feasibility and acceptability of APRETUDE for MSM and TGM.	• Patient Study Participants' (PSPs) mean FIM and Acceptability of Intervention Measure (AIM) scores as well as IS questionnaire responses at BL, M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI) and by study arm, clinic characteristics, initiation method (e.g., OLI vs. DTI)	• To evaluate feasibility and acceptability of APRETUDE for MSM and TGM.	• Patient Study Participants' (PSPs) mean FIM and Acceptability of Intervention Measure (AIM) scores as well as ~~IS~~ **implementation science** questionnaire (ISQ) responses at BL, M7(OLI)/M6(DTI) and M13(OLI)/M12(D	

		and patient subgroups (e.g., race/ethnicity, gender). • Change from baseline in PSPs' AIM and FIM scores as well as IS questionnaire responses FIM score at M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI) by study arm, clinic characteristics, and patient subgroups • PSPs perception of facilitators and barriers to feasibility and acceptability of APRETUDE by SSI through M13(OLI)/M12(DTI) by patient subgroups		TI) ~~and by study arm, clinic characteristics, initiation method (e.g., OLI vs. DTI) and patient subgroups (e.g., race/ethnicity, gender)~~. • Change from baseline in PSPs' AIM and FIM scores as well as IS**Q** ~~questionnaire~~ responses FIM score at M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI) ~~by study arm, clinic characteristics, and patient subgroups~~. • PSPs perception of facilitators and barriers to feasibility and acceptability of APRETUDE by	

	• To evaluate feasibility and acceptability of telehealth delivery for APRETUDE administration by clinical staff.	• SSPs' mean FIM and AIM scores as well as IS questionnaire responses for telehealth delivery at BL, M5 and M13 by study arm and clinic characteristics. • Change from baseline in SSPs' FIM and AIM score as well as IS questionnaire responses for telehealth delivery at M5 and M13 by study arm and clinic characteristics. • PSPs' mean FIM and AIM scores as well as IS questionnaire responses for telehealth delivery at BL, M7(OLI)/M6(DTI)		SSI through M13(OLI)/M12(DTI) ~~by patient subgroups~~.	
			• To evaluate feasibility and acceptability of telehealth delivery for APRETUDE administration by clinical staff.	• SSPs' mean FIM and AIM scores as well as IS**Q** ~~questionnaire~~ responses for telehealth delivery at BL, M5 and M13 ~~by study arm and clinic characteristics~~. • Change from baseline in SSPs' FIM and AIM score as well as IS**Q** ~~questionnaire~~ responses for telehealth delivery at M5 and M13 ~~by study arm and clinic characteristics~~. • PSPs' mean FIM and AIM scores as well as IS**Q** ~~questionnaire~~	

		and M13(OLI)/M12(DTI) by study arm, clinic characteristics, and patient subgroups. • Change from baseline in PSPs' FIM and AIM scores as well as ISQ responses for telehealth delivery at M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI) by study arm, clinic characteristics, and patient subgroups • SSPs and PSPs perception of facilitators and barriers to feasibility and acceptability of telehealth use assessed by semi-structured qualitative		responses for telehealth delivery at BL, M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI) ~~by study arm, clinic characteristics, and patient subgroups~~. • Change from baseline in PSPs' FIM and AIM scores as well as ISQ responses for telehealth delivery at M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI) ~~by study arm, clinic characteristics, and patient subgroups~~ • SSPs and PSPs perception of facilitators and barriers to	

		interviews (SSIs), FRAME-IS and facilitation calls through M13 and M13(OLI)/M12(DTI), by patient subgroups, respectively		feasibility and acceptability of telehealth use ~~assessed by semi-structured qualitative interviews (SSIs), FRAME-IS and facilitation calls~~ through M13 and M13(OLI)/M12(DTI), ~~by patient subgroups, respectively~~	
	• To evaluate acceptability and utility of DI compared to RI for APRETUDE administration	• SSPs' mean AIM score and IS questionnaire responses at BL, M5 and M13 by study arm, clinic characteristics and implementation strategy • Change from baseline in SSPs' AIM score and IS questionnaire responses at M5 and M13 by study arm, clinic characteristics and implementation strategy • PSPs' mean AIM score and ISQ	• To evaluate acceptability and utility of DI compared to RI for APRETUDE administration	• ~~SSPs' mean AIM score and IS~~**Q** ~~questionnaire~~ responses at BL, M5 and M13 ~~by study arm, clinic characteristics and implementation strategy~~ • ~~Change from baseline in SSPs' AIM score and IS~~**Q** ~~questionnaire~~ responses at M5 and M13 ~~by study~~	

		responses by implementation strategy (e.g., transportation support, designated injection days) at BL, M7(OLI)/M6(DTI) . and M13(OLI)/M12(DTI) • Proportion of SSPs and PSPs that respond in agreement on relevant items on the ISQ that each implementation strategy is fit for use through M13 and M13(OLI)/M12(DTI), respectively, and by study arm, clinic characteristics and patient subgroups • SSPs perceptions of utility of implementation		~~arm, clinic characteristics and implementation strategy~~ • PSPs' mean AIM score and ISQ responses by implementation strategy ~~(e.g., transportation support, designated injection days)~~ at BL, M7(OLI)/M6(DTI). and M13(OLI)/M12(DTI) • Proportion of SSPs and PSPs that respond in agreement on relevant items on the ISQ that each implementation strategy is fit for use through M13 and M13(OLI)/M12(DTI), respectively,	

		strategies and facilitators and barriers to acceptability of RI and DI through SSIs, ISQ FRAME-IS, IMC, and facilitation calls through M13 and by SSP characteristics • PSPs perceptions of utility of implementation strategies through SSIs through M13 and by patient subgroups		~~and by study arm, clinic characteristics and patient subgroups~~ • SSPs perceptions of utility of implementation strategies and facilitators and barriers to acceptability of RI and DI ~~through SSIs, ISQ FRAME-IS, IMC, and facilitation calls~~ through M13 ~~and by SSP characteristics~~ • PSPs perceptions of utility of implementation strategies through SSIs through M13 ~~and by patient subgroups~~	
	• To evaluate fidelity to injection and dosing window	• Proportion of injections occurring within target window from target date (-7 days for Injection dose 2 and ± 7 days of target date for subsequent injections) through M13 and by study	• To evaluate fidelity to	• Proportion of injections occurring within target window	

		arm, clinic characteristics, and patient subgroups • Proportion of PSPs completing target number of injections through M13 and by patient subgroups • PSPs and SSPs perception of barriers and facilitators to fidelity to injections as assessed by SSIs, FRAME-IS, IMC, facilitation calls and ISQ through M13 and by patient and provider subgroups	injection and dosing window	from target date (± 7 days **for target date of** Injection dose 2 and ~~± 7 days of target date for~~ subsequent injections) through M13 ~~and by study arm, clinic characteristics, and patient subgroups~~ ~~•~~ Proportion of PSPs completing target number of injections through M13 ~~and by patient subgroups~~ • PSPs and SSPs perception of barriers and facilitators to fidelity to injections ~~as assessed by SSIs, FRAME-IS, IMC, facilitation calls and ISQ~~ through	
	• To evaluate fidelity and reach of client Sexual Health Assessment	• Proportion of MSM and TGM who take the Sexual Health Assessment through M13 and by clinic			

		characteristics, patient subgroups, and service delivery method (e.g., telehealth vs. face-to-face in clinic) • Proportion of MSM & TGM who report having had sex in the last 6 months through M13 on the Sexual Health Assessment by service delivery method • Proportion of MSM & TGM who expressed interest in PrEP or never heard of PrEP out of those who report having had sex in the last 6 months through M13 by service delivery method • Proportion of PSPs who initiate		M13 and ~~by patient and provider subgroups~~	
			• To evaluate fidelity and reach of client Sexual Health Assessment	• ~~•~~ Proportion of MSM and TGM who take the Sexual Health Assessment through M13 ~~and by clinic characteristics, patient subgroups, and service delivery method (e.g., telehealth vs. face-to-face in clinic)~~ • ~~•~~ Proportion of MSM & TGM who report having had sex in the last 6 months through M13 on the Sexual Health Assessment ~~by service delivery method~~	

		APRETUDE after taking the Sexual Health Assessment through M13 and by clinic characteristics, patient subgroups, and service delivery method • SSPs and PSPs perceptions of Sexual Health Assessment assessed by SSIs, FRAME-IS, IMC, facilitation calls and ISQ through M13 and by patient and provider subgroups		• Proportion of MSM & TGM who expressed interest in PrEP or never heard of PrEP out of those who report having had sex in the last 6 months through M13 ~~by service delivery method~~ • Proportion of PSPs who initiate APRETUDE after taking the Sexual Health Assessment through M13 ~~and by clinic characteristics, patient subgroups, and service delivery method~~ • SSPs and PSPs perceptions of Sexual Health Assessment ~~assessed by SSIs, FRAME-IS, IMC, facilitation calls~~	
	• To evaluate adaptations to any implementation strategies used in clinics to include but not limited to modifications to toolkits, RI and DI to support	• SSIs, ISQ, FRAME-IS, IMC and facilitation calls with SSPs through M13 and SSIs and ISQ with PSPs through M13(OLI)/M12(DTI)			

	APRETUDE implementation			~~and ISQ~~ through M13 and ~~by patient and provider subgroups~~	
	• To evaluate switch from oral PrEP to APRETUDE	• Proportion of PSPs with history of PrEP use that complete the Sexual Health Assessment and ISQ and start APRETUDE through M13 and by patient subgroups • PSPs reasons for choosing APRETUDE, including switching, as assessed by SSIs and ISQ questionnaires and by patient subgroups	• To evaluate adaptations to any implementation strategies used in clinics to include but not limited to modifications to toolkits, RI and DI to support APRETUDE implementation	~~•~~ Proportion of PSPs with history of PrEP use that complete the Sexual Health Assessment and ISQ and start APRETUDE through M13 ~~and by patient subgroups~~ • PSPs reasons for choosing APRETUDE, including switching, as assessed by SSIs and ISQ ~~questionnaires and by patient subgroups~~	
	• To evaluate perceptions, barriers and facilitators with SSPs and PSPs	• SSIs, ISQ, FRAME-IS, IMC and facilitation calls assessed with SSPs through M13	• To evaluate switch from oral	• Proportion of PSPs with history	

		and IS questionnaires and SSIs with PSPs through M13(OLI)/M12(DTI)	PrEP to APRETUDE	of PrEP use that complete the Sexual Health Assessment and ISQ and start APRETUDE through M13 ~~and by patient subgroups~~ • PSPs reasons for choosing APRETUDE, including switching, as assessed by SSIs and ISQ ~~questionnaires and by patient subgroups~~	
	• Other / Tertiary CCI [redacted]		• To evaluate perceptions, barriers and facilitators with SSPs and PSPs	• ~~SSIs, ISQ, FRAME-IS, IMC and facilitation calls assessed with SSPs through M13 and IS questionnaires and SSIs with PSPs through~~	

	CCI [redacted]	~~M13(OLI)/M12(DTI)~~ • **PSPs and SSPs perception of barriers and facilitators through M13.**	
		• Other / Tertiary	
		CCI [redacted]	

CCI

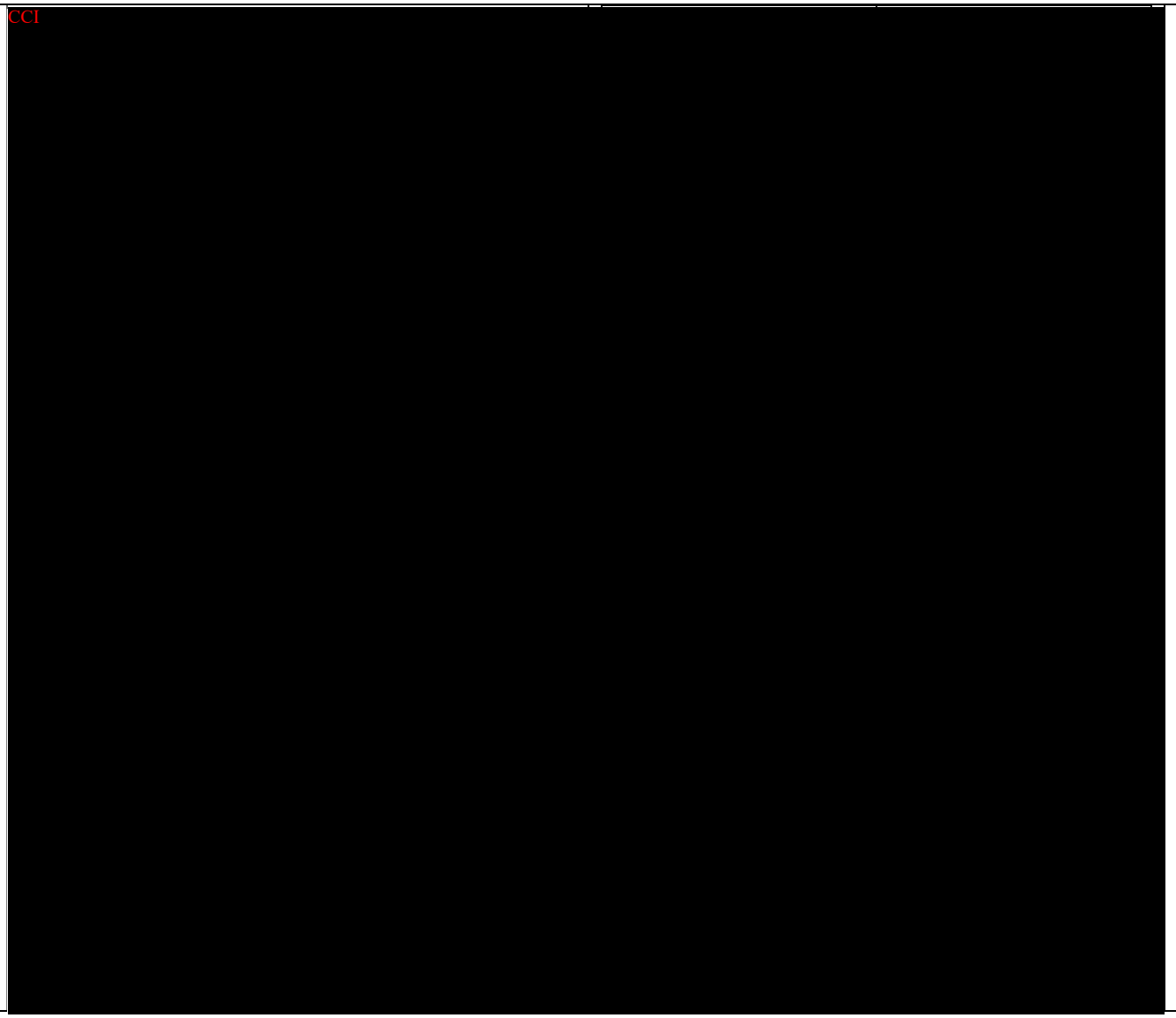
CCI

[redacted]

CCI

[redacted]

CCI



	CCI [redacted]		
Section 3.2 – Study Population	Approximately 220 PSPs will be enrolled. We aim for a total of 50% of the enrolled PSPs to be Black and Latino. We also aim for a total of 2-4% of the enrolled PSPs to be TGM, at a minimum. The number of SSPs will vary by site and approximately 5 per site will be included.	Approximately 220 PSPs will be enrolled. We aim for a**t least** ~~total of~~ 50% of the enrolled PSPs to be Black ~~and~~ **or** Latino. ~~We also aim for a total of 2-4% of the enrolled PSPs to be TGM, at a minimum.~~ **Of the total PSPs enrolled, we aim for at least 2-4% to be TGM.** The number of SSPs will vary by site and approximately 5 per site will be included.	Text updated to clarify diversity targets of the study to ensure adequate enrolment of underrepresented populations.
Section 3.3.1 – PSPs	PSPs meeting all eligibility criteria at the screening/enrolment visit will sign the informed consent form at the site or through virtual administration. Screen failures are defined as PSPs who consent to participate in the study but are not subsequently entered in the study. A minimum set of screen failure information will be collected including demography, screen failure details, eligibility criteria, and any serious adverse events.	PSPs meeting all eligibility criteria at the screening/enrolment visit will sign the informed consent form at the site or through virtual administration. Screen failures are defined as PSPs who consent to participate in the study but are not subsequently entered in the study. A minimum set of screen failure information will be collected including demography, screen failure details, eligibility criteria, and any serious adverse	Clarified re-screening options for potential PSPs who screen fail due to delays in benefits verification with no other screening procedures having been performed. Re-screening for those

	Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time within 4 weeks of the original screening; informed consent will need to be reviewed and re-signed for each rescreen. Subjects will be issued a new ID number for every screening/re-screening event. SSPs will not be captured for screen failure reporting.	events. Individuals who do not meet the criteria for participation in this study (screen failure) **post benefits verification** may be rescreened one time within 4 weeks of the **date they were determined to have screen failed. Individuals who screen fail due to benefits verification exceeding the 90-day screening window, with no other screening assessments having been performed, may be rescreened once, to take place any time after benefits verification has been obtained** ~~original screening~~; informed consent will need to be reviewed and re-signed for each rescreen. Subjects will be issued a new ID number for every screening/re-screening event. SSPs will not be captured for screen failure reporting.	potential PSPs will be permitted any time after benefits verification is confirmed. For any other screen failure reason, the 4-week window for re-screening still applies.
Section 4.1.2 Dynamic Implementation	Detail information on the strategies is given in the SRM.	~~Detail information on the strategies is given in the SRM.~~	Text removed as information on strategies are captured by the implementation science vendor.
Section 4.1.3.1 – Group and 1:1 Facilitation	Group facilitation should occur quarterly,	Group facilitation should occur quarterly, **as needed.**	Added information to clarify when group facilitation should occur.

Section 5.6 – Qualitative Analyses	Qualitative data collection and analyses for both SSPs and PSPs will be informed by the study frameworks – CFIR and Proctor outcomes framework. The qualitative data are embedded within the quantitative outcomes of the study for expansion and triangulation of data. All qualitative data will be recorded, transcribed, translated if necessary, cleaned. Data will be entered into a qualitative data management software and any notes from calls will be compiled and analyzed. The Implementation Science vendor will be responsible for coding all qualitative assessments for use in the evaluation of the study outcomes. Established procedures to enhance validity will be used, including development of an audit trail documenting analytical decisions, agreeing on a threshold for rater agreement, and documenting coding decisions.	Qualitative data collection and analyses for both SSPs and PSPs will be informed by the study frameworks – CFIR and Proctor outcomes framework. **SSPs and PSPs perceptions on implementation, including but not limited to facilitators and barriers, implementation of PrEP into routine care, quality of care, will be assessed by semi-structured qualitative interviews, implementation science questionnaire, FRAME-IS, implementation monitoring calls and facilitation calls.** The qualitative data are embedded within the quantitative outcomes of the study for expansion and triangulation of data. All qualitative data will be recorded, transcribed, translated if necessary, cleaned. Data will be entered into a qualitative data management software and any notes from calls will be compiled and analyzed. The Implementation Science vendor will be responsible for coding all qualitative assessments for use in the evaluation of the study outcomes. Established procedures to enhance validity will be used, including development of an audit trail documenting analytical decisions, agreeing on a threshold for rater agreement, and documenting coding decisions.	Added information on the types of assessments to be used to analyse SSP and PSPs perceptions on implementation.

Section 6.2 Participant Confidentiality Section 6.2.1 - PSPs	Not applicable	**Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, in order to meet the study objectives and to determine if the trial participants are truly representative of the impacted population.**	Added new mandatory GSK/ViiV protocol text regarding collection of sensitive information such as sex, race and ethnicity data as part of the study.
Section 6.3 – Informed Consent Process	The PrEP Provider or his/her representative will explain the nature of the study to the participant, or their legally authorized representative and answer all questions regarding the study. • PSPs must be informed that their participation is voluntary. PSPs 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 study	The PrEP Provider or his/her representative will explain the nature of the study, **including the risks and benefits**, to the participant, or their legally authorized representative and answer all questions regarding the study. • **Potential** PSPs must be informed that their participation is voluntary. PSPs will be required to **physically or electronically** 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~~ **physical or electronic** informed consent was obtained before the participant was enrolled in the study and the date the	Removed reference to written consent and added clarification that consent may be given either physically or electronically

	site authorized person obtaining the informed consent must also sign the ICF. • PSPs 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.	~~written~~ **physical or electronic** consent was obtained. The study site authorized person obtaining the informed consent must also sign the ICF. • PSPs must be re-consented to the most current version of the ICF(s) during their participation in the study. • A **physical or electronic** copy of the ICF(s) must be provided to the participant or their legally authorized representative.	
Section 9.1.1 – 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 and 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. • 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	• All AEs that meet the criteria for documentation listed in Section 9.1, and 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 and 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. • **A poststudy AE/SAE is defined as any event that occurs outside of the**	Section updated to incorporate new mandatory GSK protocol language for AE reporting.

	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.	**AE/SAE reporting period defined earlier in this Section 9.1.1.** • 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, **the PrEP Provider must record it in the medical records. If the PrEP Provider** ~~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.	
Section 11.1 Annex 1: Schedule of Activities – direct to injection **Section 11.2**	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	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. **All other** ~~S~~screening/eligibility procedures (excluding informed consent) should ~~not~~ **only** be performed ~~prior to~~ **after** receiving this **benefits** 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	Based on feedback from sites, wording of this footnote has been clarified. PSPs should consent to the study and a benefits verification check should be completed and benefits confirmed before any other screening/eligibility

Annex 2: Schedule of Activities – Optional oral lead in	form (ICF), 2) Benefits verification, as required, 3) Confirm Inclusion and Exclusion criteria, 4) Demography 5) Medical History, including history of HCV 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 3.3.1 for details on re-screening for PSPs who fail screening. **Patient Study Participants** Participants baseline questionnaires and interviews should be completed within two weeks prior to or on their D1 visit and before receiving the 1st APRETUDE injection. Approximately 3 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 race/ethnicity, prior PrEP use. Participant Interviews Notes: Interviews will be completed on a subset of PSPs (see Section 4.1.3.1). Window within 2 weeks before or 2 weeks following study visit.	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 HCV 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 3.3.1 for details on re-screening for PSPs who fail screening. **Patient Study Participants** **PSP** baseline questionnaires ~~and interviews~~ should be completed within two weeks prior to or on their D1 visit and before receiving the 1st APRETUDE injection. **Participants interviews should be completed within two weeks prior to or two weeks following their D1 visit and within two weeks prior to or two weeks following the target dates for their D4 and D7 visits.** Approximately 3 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	procedure is performed. Removed and added text to clarify timing of participant questionnaires and interviews

	Staff Study Participants 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. SSP questionnaires and/or interviews can be completed within 3 of study visits.	characteristics, such as race/ethnicity, prior PrEP use. All additional study visits, including those where questionnaires and/or interviews are administered at M6 and M12, will be anchored off of each participants M1 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. **Staff Study Participants** For sites with both OLI and DTI participants, M4/M5 visit will be defined **by the target date** 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 **by the target date** when at least 1 participant, at their respective site, has completed their M12(DTI)/M13(OLI) study visit (Dose 7 visit), whichever comes first. **Interim and final** SSP questionnaires and/or interviews can be completed **within 3 weeks prior to or 3 weeks after** study visits.	

Section 11.4.5 Reporting of SAE to the Sponsor – Subsection SAE Reporting to the Sponsor via Electronic Data Collection Tool	Not applicable	New bullet point: • **If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.**	This section has been updated to include new GSK mandatory protocol language.

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	adverse event
AIM	Acceptability of Intervention Measure
ART	Antiretroviral therapy
CAB LA for PrEP	(hereafter referred to as APRETUDE)
CAB PrEP	Oral Cabotegravir (CAB) tablets and CAB long acting (LA) extended-release suspension for injection for pre-exposure prophylaxis (PrEP)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus Disease of 2019
DDI	drug-drug interaction
DI	dynamic implementation
DSMB	Data and Safety Monitoring Board
DTI	direct to injection
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
FIM	Feasibility of Intervention Measure
FTC	Emtricitabine
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HR	Hazard ratio
ICF	informed consent form
ID	Identifier
IM	Intramuscular
IMC	Implementation monitoring calls
IRB	Institutional review board
IS	Implementation science
ISQ	Implementation science questionnaire
ISF	Investigator Site File
LA	long acting
LMP	Last menstrual period
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
RI	routine implementation

RPV	rilpivirine
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SSI	semi-structured interview
SSP	Staff study participant
STI	sexually transmitted infections
TDF	tenofovir disoproxil fumarate
TGM	Transgender men
TGW	Transgender women
U.S.	United States
USPI	United States Prescribing Information
VHC	ViiV Healthcare

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Abstract

Background/Rationale: Oral Cabotegravir (CAB) tablets and CAB long acting (LA) extended-release suspension for injection for pre-exposure prophylaxis (PrEP) has 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 efficacy of CAB LA when compared to daily, oral emtricitabine (FTC)/ tenofovir disoproxil fumarate (TDF) in cisgender men who have sex with men (MSM) and transgender women (TGW) who have sex with men and HPTN 084 demonstrated the efficacy of CAB LA when compared to daily, oral FTC/TDF in cisgender women.

CAB LA for PrEP (hereafter referred to as APRETUDE) will provide people who are at higher risk of 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 (FTC/TDF), 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) as well as expanding an injectable delivery to alternative models of care that are already used for oral PrEP (e.g., telemedicine-supported PrEP delivery and community-based organization delivered PrEP).

In this study, an innovative set of implementation strategies will be used to address anticipated challenges associated with feasibility of APRETUDE delivery.

Objectives: The primary objective is to evaluate the feasibility of dynamic implementation (DI) compared to routine implementation (RI) for APRETUDE administration.

The secondary objectives include

- To evaluate change in feasibility of RI and DI for APRETUDE administration
- To evaluate feasibility and acceptability for APRETUDE for MSM and transgender men (TGM).
- To evaluate feasibility and acceptability of telehealth delivery for APRETUDE administration by clinical staff.
- To evaluate acceptability and utility of DI compared to RI for APRETUDE administration
- To evaluate fidelity to injection and dosing window

- To evaluate fidelity and reach of client Sexual Health Assessments for APRETUDE
- To evaluate adaptations to any implementation strategies used in clinics to include, but not limited to, modifications to toolkits, RI and DI to support APRETUDE implementation
- To evaluate switch from oral PrEP to APRETUDE
- To evaluate perceptions, barriers and facilitators with Staff Study Participants (SSPs) and Patient Study Participants (PSPs)

Study Design: This post-approval, Phase 4 study is designed to evaluate the impact of two implementation strategy conditions – dynamic implementation and routine implementation – on the feasibility of delivering APRETUDE in high and low volume current PrEP sites for MSM and TGM over 12 months. Approximately 18 sites will be randomized 2:1 in the Dynamic (DI) or Routine (RI) implementation arms. Randomization will occur at the level of study sites and the study will enroll the staff at the study site (who are enrolled as "Staff Study Participants"). Approximately 220 HIV negative individuals will be enrolled once CAB PrEP is prescribed to them ("Patient Study Participants"); at least 50% will be Black or Latino. Patients 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 Centers for Disease Control and Prevention (CDC) clinical management guidelines for PrEP [Centers for Disease Control and Prevention, 2021] and APRETUDE USPI using sites local laboratories [APRETUDE, 2021].

Sites randomized to RI will have access to the standard CAB LA for PrEP toolkits for providers and patients to use as needed. Sites randomized to DI will receive enhanced toolkits for providers and patients, a digital health end to end implementation strategy, and implementation facilitation.

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 feasibility is SSPs' mean FIM score at Month 13 under Dynamic Implementation (DI) arm and Routine Implementation (RI) arm respectively, and the difference of SSPs' mean FIM scores between two arms at Month 13. Descriptive statistics including 95% confidence intervals (CI) 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 subject level, the stratification analysis will be performed at the site level to evaluate the impact of the capacity of sites (high volume vs low volume) in responding to two 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 FIM scores of SSPs at different timepoints, the change in FIM scores of each item from baseline will be analyzed at the designated timepoints. For the specific Telehealth implementation strategy on SSPs, the subgroup analysis on FIM scores including change from baseline will be conducted.

The FIM 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, utility, reach, fidelity and adaptations will be similar to that of the feasibility endpoints.

1. BACKGROUND AND RATIONALE

1.1. Background

Cabotegravir (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 long acting (LA) formulation of rilpivirine (RPV LA- Janssen), has been approved in countries including the U.S., European Union (EU), Canada and Australia 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, have been 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 portion 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 APRETUDE when compared to daily, oral FTC/TDF (Hazard Ration [HR] 0.34, two-sided superiority p = 0.0005) in MSM and TGW and that participants randomized to the active FTC/TDF group be offered APRETUDE [HIV Prevention Trials Network, 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 efficacy of APRETUDE when compared to daily, oral FTC/TDF (HR 0.11, two-sided superiority p = 0.000042) in cisgender women and that participants randomized to the active FTC/TDF group be offered APRETUDE [HIV Prevention Trials Network, 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 higher risk of HIV acquisition with a new prevention option and could contribute to reducing disparities in HIV infections and PrEP utilization. Of the 37,000 new cases of HIV infection in the US, 65% were among men

who have sex with men (MSM) and among all MSM, 67% of diagnoses were among African American/Black and Hispanic/Latino MSM [Centers for Disease Control and Prevention, 2021]

Centers for Disease Control and Prevention, 2021; Centers for Disease Control and Prevention, 2018]. The Southern US accounted for 50% of all diagnoses of HIV infection among MSM, which the largest being among African American/Black (48%), followed by Hispanic/Latino (26%) and White (23%) MSM. In terms of PrEP, Centers for Disease Control and Prevention (CDC) reported PrEP awareness and use were lower in Black and Hispanic MSM as compared to White MSM [Jones, 2021; Kanny, 2019]. The Southern US represented only 30 percent of all PrEP users despite accounting for more than half of new HIV diagnoses in the country [Sullivan, 2018]. Further, 3.2% of transgender men (TGM) are living with HIV but TGM has largely been left out of the HIV discourse [Centers for Disease Control and Prevention, 2019].

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]. CAB PrEP has several appealing features that might overcome a few of these challenges, including superiority, more discretion, and less frequent dosing when compared to a daily oral PrEP regimen (FTC/TDF); CAB PrEP's dosing frequency 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 CAB PrEP will require layering onto existing PrEP models of care (e.g., clinics and health centers) as well as expanding to alternative models of care (e.g., pharmacy-based PrEP, telemedicine-supported PrEP delivery and community-based organization delivered PrEP) in order to reach populations vulnerable to HIV, especially in the Southern US [Sullivan, 2018]. 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 MSM [Smith, 2016]. Clinical CBOs are more prepared to support expansion of biomedical interventions than nonclinical CBOs [Smith, 2016]. The Coronavirus Disease of 2019 (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 CAB PrEP.

As CAB PrEP is introduced to consumers, early development and implementation of strategies to addresses challenges associated with feasibility of its delivery will be

important to removing barriers to uptake and persistence by populations vulnerable to HIV.

1.2. Rationale

This post-approval, Phase 4 study is designed to evaluate the impact of two implementation strategy conditions – dynamic implementation and routine implementation – on the feasibility of delivering APRETUDE in high and low volume current PrEP sites for MSM and transgender men over 12 months. Volume will be defined using all clinic feasibility data. One or a combination of the following approaches will be considered: absolute PrEP volume; average number of established PrEP patients; PrEP to need ratio vs. clinic ratio; and established providers of PrEP services (e.g., hub, referral site) vs. new to PrEP sites.

Clinical sites will be randomized 2:1 in the Dynamic (DI) or Routine (RI) implementation arms. Clinics randomized to RI will have access to the standard toolkits for providers and patients that will be available for APRETUDE to use as needed. Clinics randomized to DI will receive enhanced toolkits for providers and patients, a digital health end to end implementation strategy, and implementation facilitation.

Implementation science methodology using both quantitative and qualitative measures will be used to assess whether DI as opposed to RI results in higher feasibility in delivering APRETUDE. The study will also evaluate reach, utility, fidelity to and acceptability of the implementation strategies; 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" and the staff at the study site (who are enrolled as "Staff Study Participants") -- see below for definitions of participants). Clinical data will be collected from Patient Study Participants to monitor safety and efficacy (Refer to Section 7; Section 8 and Section 9).

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 (Refer to Section 7 and Section 8).

The study will examine the impact of the dynamic and routine implementation on the delivery of CAB PrEP in high and low volume current PrEP sites. As a result, the study will identify strategies that are or are not successful in the delivery of CAB PrEP.

1.3. 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 United States Prescribing Information [APRETUDE, 2021].

1.3.1. Overall Benefit: Risk Conclusion

The results of this study are anticipated to be beneficial or useful for individuals receiving CAB PrEP and physicians providing CAB PrEP.

2. OBJECTIVES AND ENDPOINTS

• Objectives	• Endpoints
• Primary	
• To evaluate feasibility of dynamic implementation (DI) compared to routine implementation (RI) for APRETUDE administration.	• Staff study participants' (SSPs) mean Feasibility of Intervention Measure (FIM) score at M13[1].
• Secondary	•
• To evaluate change in feasibility of RI and DI for APRETUDE administration	• Change from baseline in SSPs' FIM score at M5 and M13. • SSPs perceptions of facilitators and barriers to RI and DI and overall implementation of PrEP into routine care assessed through M13.
• To evaluate feasibility and acceptability of APRETUDE for MSM and TGM.	• Patient Study Participants' (PSPs) mean FIM and Acceptability of Intervention Measure (AIM) scores as well as implementation science questionnaire (ISQ) responses at BL, M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI). • Change from baseline in PSPs' AIM and FIM scores as well as ISQ responses FIM score at M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI). • PSPs perception of facilitators and barriers to feasibility and acceptability of APRETUDE through M13(OLI)/M12(DTI).
• To evaluate feasibility and acceptability of telehealth delivery for APRETUDE administration by clinical staff.	• SSPs' mean FIM and AIM scores as well as ISQ responses for telehealth delivery at BL, M5 and M13. • Change from baseline in SSPs' FIM and AIM score as well as ISQ responses for telehealth delivery at M5 and M13 .

• Objectives	• Endpoints
	• PSPs' mean FIM and AIM scores as well as ISQ responses for telehealth delivery at BL, M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI) • Change from baseline in PSPs' FIM and AIM scores as well as ISQ responses for telehealth delivery at M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI). • SSPs and PSPs perception of facilitators and barriers to feasibility and acceptability of telehealth use through M13 and M13(OLI)/M12(DTI) respectively.
• To evaluate acceptability and utility of DI compared to RI for APRETUDE administration	• SSPs' mean AIM score and ISQ responses at BL, M5 and M13 . • Change from baseline in SSPs' AIM score and ISQ responses at M5 and M13. • PSPs' mean AIM score and ISQ responses by implementation strategy at BL, M7(OLI)/M6(DTI). and M13(OLI)/M12(DTI) • Change from baseline in PSPs' mean AIM score and ISQ responses by implementation strategy at M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI) • Proportion of SSPs and PSPs that respond in agreement on relevant items on the ISQ that each implementation strategy is fit for use through M13 and M13(OLI)/M12(DTI), respectively. • SSPs perceptions of utility of implementation strategies and facilitators and barriers to acceptability of RI and DI through M13

• Objectives	• Endpoints
	• PSPs perceptions of utility of implementation strategies through SSIs through M13.
• To evaluate fidelity to injection and dosing window	• Proportion of injections occurring within target window from target date (±7 days for target date of Injection dose 2 and subsequent injections) through M13 • Proportion of PSPs completing target number of injections through M13 • PSPs and SSPs perception of barriers and facilitators to fidelity to injections through M13
• To evaluate fidelity and reach of client Sexual Health Assessment	• Proportion of site staff who administer Sexual Health Assessment through M13. • Proportion of eligible PSPs for which Sexual Health Assessment are administered through M13 • Proportion of MSM and TGM who take the Sexual Health Assessment through M13 • Proportion of MSM & TGM who report having had sex in the last 6 months through M13 on the Sexual Health Assessment • Proportion of MSM & TGM who expressed interest in PrEP or never heard of PrEP out of those who report having had sex in the last 6 months through M13 • Proportion of PSPs who initiate APRETUDE after taking the Sexual Health Assessment through M13 • SSPs and PSPs perceptions of Sexual Health Assessment through M13
• To evaluate adaptations to any implementation strategies used in clinics to include but not limited to	• Summarize components adapted and changes made using FRAME-IS at

• Objectives	• Endpoints
modifications to toolkits, RI and DI to support APRETUDE implementation	pre-implementation and monthly through M13 • SSPs and PSPs perceptions of adaptations to implementation strategies through M13
• To evaluate switch from oral PrEP to APRETUDE	• Proportion of PSPs with history of PrEP use that complete the Sexual Health Assessment and ISQ and start APRETUDE through M13 • PSPs reasons for choosing APRETUDE, including switching, as assessed by SSIs and ISQ
• To evaluate perceptions, barriers and facilitators with SSPs and PSPs	• PSPs and SSPs perception of barriers and facilitators through M13.
• Other / Tertiary	

CCI

[redacted]

• Objectives	• Endpoints

CCI

[redacted]

• Objectives	• Endpoints

CCI

[redacted]

• Objectives	• Endpoints
CCI [redacted]	

- [1] If the site has only DTI patients, endpoints will be a month prior for SSPs.

3. RESEARCH DESIGN

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

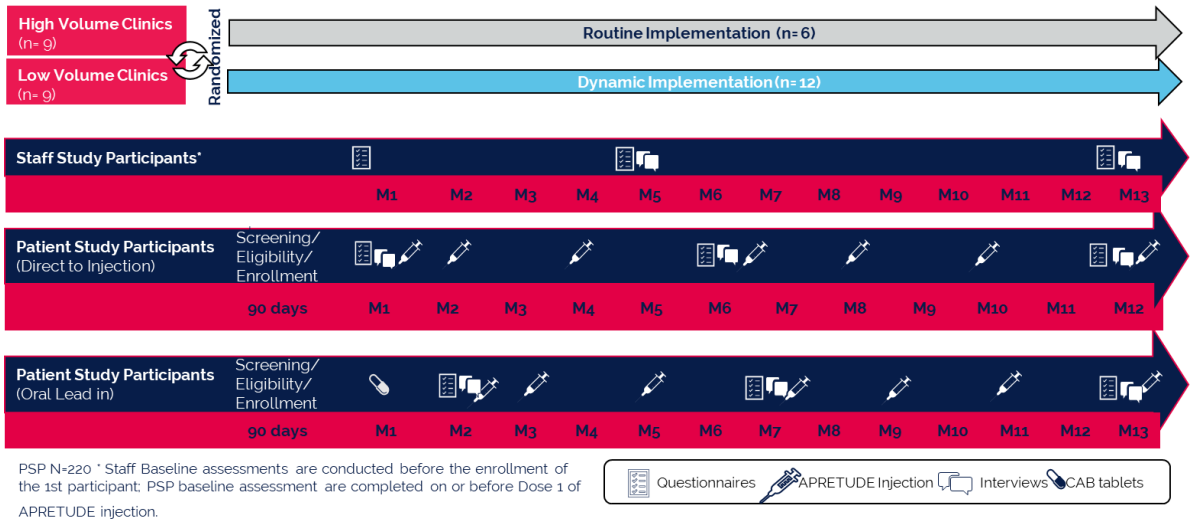
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

3.1. Study Design

This is a Phase 4, randomized, open-label, two-arm study evaluating the impact of two implementation strategy conditions – dynamic implementation and routine implementation – on the delivery of CAB PrEP in low and high-volume PrEP sites in the U.S. for MSM and Transgender men ≥ 18 years of age. MSM and transgender men who tested HIV-1 negative at the sites prior to initiation of CAB PrEP (Section 3.2.1) will be enrolled. Approximately eighteen clinics – about 9 high and about 9 low volume – will be randomized 2:1 to either dynamic implementation or routine implementation. This study is being conducted following FDA approval and commercial availability of CAB PrEP in the U.S.

Eligible and consenting PSPs will be followed for 12 calendar 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. The screening period is followed by a 11-month or 12-month administration period of CAB PrEP depending on whether an optional 1-month oral lead-in of CAB tablets for PrEP is administered, followed by APRETUDE IM injections every two months after the one-time loading dose (i.e., first 2 IM doses 1 month apart and 2 months apart thereafter). All PSPs will receive a total of 7 APRETUDE IM injections, with the last IM injection visit being their last study visit. After 11-month (direct to injection) or 12-month (with OLI) treatment period, PSPs will complete the study and will be offered PrEP regimen as per site standard of care. When PSPs complete their M12/M13 assessments, irrespective of missed injections, they will be a completer. Consenting SSPs at the site will participate in study quantitative and qualitative study assessments to evaluate the impact of the two implementation strategy conditions on the feasibility of delivering APRETUDE. When SSPs completes their M13 study assessments, they will be a completer. The end of study is defined when the last PSP and SSP have completed their implementation science assessments. For a detailed Schedule of Activities (SoA) refer to ANNEX 1 and ANNEX 2. CAB PrEP dosing information can be found in the prescribing information for CAB PrEP.

Figure 1 Study Design Schematic



3.2. Study Population

Approximately 220 PSPs will be enrolled. We aim for at least 50% of the enrolled PSPs to be Black or Latino. Of the total PSPs enrolled, we aim for at least 2-4% to be TGM. The number of SSPs will vary by site and approximately 5 per site will be included.

During the screening period, PSPs who enroll into the study will complete informed consent and confirmation of inclusion and exclusion criteria will be conducted. Each PSP being screened for study enrollment evaluation will be assigned a PSP number at the screening visit (refer to the SRM for details). Completion of study assessments will occur prior to receipt of Dose 1(D1) of intramuscular (IM) injections.

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 subject visit.

3.2.1. Eligibility Criteria

3.2.1.1. Inclusion Criteria for PSP

Age:

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

Type of Participant and Disease Characteristics

2 HIV negative test result at screening

3 No prior history of receiving CAB PrEP (Note: prior or active use of non-CAB PrEP ([FTC/TDF or FTC/TAF]) 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 Men who have sex with Men or Transgender Men.

Informed Consent

6 Capable of giving signed informed consent as described in Section 6.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

3.2.1.2. Exclusion Criteria for PSP

Medical Conditions

1 HIV indeterminate or positive test result during screening and prior to initiation of CAB PrEP (CAB tablets for PrEP or APRETUDE).

Prior/Concomitant Therapy

2 Refer to the current U.S. Prescribing Information for CAB PrEP, i.e., for CAB tablets for PrEP and APRETUDE

Prior/Concurrent Clinical Study Experience

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

Other exclusions

4 Cis-gender or Transgender female

5 As dictated in the Prescribing Information for CAB PrEP in consultation with the prescriber.

3.2.1.3. Inclusion Criteria for SSPs

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

7 They are site employees responsible for administrative (for administrative SSPs)/ or clinical (for clinical SSPs) aspects of offering and administering CAB PrEP at the site.

8 Has the required qualifications according to their role and delegated the appropriate responsibilities by the PrEP Provider.

9 Be able to understand and comply with protocol requirements, instructions, and restrictions.

10 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.

3.2.1.4. Exclusion Criteria for SSPs

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

6 Engaged or planned engagement in an implementation science study with similar strategies on long acting PrEP injectables at any time during the study.

7 SSP does not have adequate resource to complete study assessments.

3.3. Study Groups and Duration

This study will enroll the following groups: MSM and transgender men who are not living with HIV (as PSPs) and staff at sites offering PrEP (i.e., as SSPs). Sites will be randomized to RI or DI prior to study participant enrolment.

Assessments can be found in ANNEX 1 and ANNEX 2.

3.3.1. PSPs

MSM and transgender men who are HIV negative prior to initiation of CAB PrEP and who have either not previously received PrEP (i.e., PrEP naïve) or are current or prior users of oral PrEP (e.g., FTC/TDF, FTC/TAF, generic FTC/TDF) and meet CDC eligibility for PrEP initiation, including documentation of a negative HIV test per CDC guidelines [Centers for Disease Control and Prevention, 2021], are allowed in the study as PSPs.

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.

PSPs meeting all eligibility criteria at the screening/enrolment visit will sign the informed consent form at the site or through virtual administration. Screen failures are defined as PSPs who consent to participate in the study but are not subsequently entered in the study. 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) post benefits verification may be rescreened 1 time within 4 weeks of the date they were determined to have screen failed. Individuals who screen fail due to benefits verification exceeding the 90-day screening window, with no other screening assessments having been performed, may be rescreened once, to take place any time after benefits verification has been obtained; informed consent will need to be reviewed and re-signed for each rescreen. Subjects will be issued a new ID number for every screening/re-screening event. SSPs will not be captured for screen failure reporting.

For PSPs receiving optional OLI, the final dose should be taken on the same day as the APRETUDE IM injections are started. CAB tablets for PrEP and APRETUDE dosing will be performed in accordance with the corresponding CAB PrEP prescribing information.

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. 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.

The total duration of study participation for PSPs is approximately 12 calendar months from the time of enrolment to the receipt of the final administration of APRETUDE IM injection. A PSP is considered to have completed the study if the PSP has finished all protocol-specified (i.e., Month 12 for PSPs who started CAB PrEP without optional OLI, and Month 13 for PSPs who started CAB PrEP with OLI) assessments and receive the last injection of APRETUDE during the study.

3.3.2. SSPs

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 questionnaires and interviews at baseline, M5 and M13; baseline questionnaires with SSPs should be completed prior to the enrolment 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. They will also participate in monthly FRAME-IS assessments. Sites in the DI 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/M1. The site will also complete demography and vital signs and required labs per clinical local standard of care.
- (See SoA for specific laboratory test results that should be documented in the eCRF, e.g., HIV testing 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 enrolment 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, 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 the monthly and every 2 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 PrEP Provider 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 [APRETUDE, 2021].
- 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

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).

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 9.3 for additional information). All study assessments and events should be kept in the PSP source documentation (refer to Section 11.7.4).

Total duration of study participation for SSPs is approximately 12 calendar months, at the time of enrollment of the last PSP at their site (questionnaires 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.

4. Implementation Research Methods

4.1. Study Arms Overview

The two study arms are routine implementation and dynamic implementation. Clinics will be randomized to the two study arms in a 2:1 distribution, whereby about 12 clinics will be in the dynamic implementation arm and about 6 clinics will be in the routine implementation arm (Note: Number of clinics may vary depending on recruitment). Clinics receiving routine implementation will receive standard provider and patient toolkits that will be available when CAB PrEP is commercially available. Clinics receiving dynamic implementation will receive enhanced toolkits, a digital health end to end implementation strategy, and implementation facilitation. An overview of the RI and DI implementation strategies are outlined in Table 1 and Table 2 in terms of six dimensions as recommended by Proctor and colleagues [Proctor, 2013]: actor, the action, action targets, dose, implementation outcomes addressed, and theoretical justification.

4.1.1. Routine Implementation

The RI arm will evaluate the feasibility of APRETUDE delivery without implementation supports. Sites randomized to RI will have access to the standard toolkits for providers and patients that will be available for APRETUDE to use as needed. An overview of example materials contain in the toolkits is provided in Table 1. Detail information on the toolkits is given in the SRM. SSPs in the RI arm will participate in study training, FRAME-IS assessments and implementation monitoring.

- **Study Training**: In preparation for the study, all SSPs and other relevant site staff will receive study training including information on safety and effectiveness of APRETUDE, study procedures, and information and/or training on implementation strategies. Study training requirements will be described in the study training plan and evidence of training will be filed in the Investigator Site File (ISF). Initial study training will be covered in the Investigator meeting, other virtual sessions, via on demand learning or and at the site initiation visits. SSPs should complete all study training applicable to their role.

- **FRAME-IS Assessments**: SSPs in the RI arm most knowledgeable of the study, clinic operations and modifications will participate in monthly FRAME-IS assessments, which are administered via email and takes maximum 15 minutes to complete. All SSPs will be asked to complete the FRAME-IS in order to understand implementation from the perspective of the different roles. The Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS) provides a systematic way of documenting and tracking modifications to implementation strategies in traditional healthcare settings, allowing for a better understanding of how the strategies influence outcomes [Miller, 2021]. The assessments will provide understanding of implementation challenges and successes as well as modifications made, if any, to overcome identified challenges at each clinical site.

- **Implementation monitoring**: Implementation monitoring focuses on understanding each site's integration of CAB PrEP rather than intervening and is not considered an implementation strategy. The information collected can be used to develop lessons-learned to promote sustainability and scale-up in future clinics. Monitoring may include brief monthly or quarterly calls with the designated site implementation lead at each RI site or a written form that assesses implementation progress. 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.

SSPs and PSPs will complete all assessments per the SoA (ANNEX 1 and ANNEX 2).

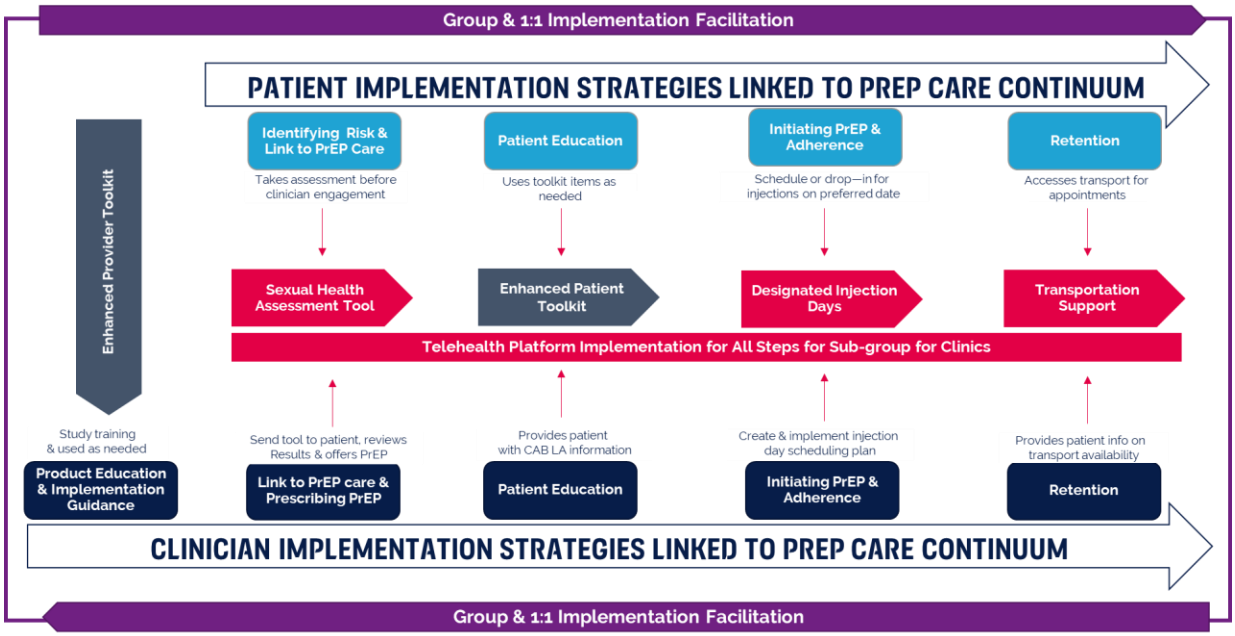
Table 1 Routine Arm Implementation Strategies

	Toolkits	
	Provider Toolkit	**Patient Toolkit**
Action	Office Starter Guide, Instructions for Use, Guidance on Pausing/Stopping, Discussion Points Checklist; Injection Education Video. Treatment Scheduler, Dosing and Admin Guide, Implementation Video, ViiV Connect Materials, Demo Packs	Patient Appointment Reminder Cards; Welcome Brochure; FAQs
Actor	ViiV developed, delivered with IS vendor support	ViiV developed, delivered with IS vendor support
Action target	Improved provider knowledge of CAB PrEP and access to implementation resources	Improve patient knowledge about CAB PrEP and support retention in care
Dose	As needed	As needed
Outcome	Feasibility, acceptability, utility	Feasibility, acceptability, utility
Justification	Clinicians needs logistic support to integrate new modality into clinics	Patients may benefit from support materials to be aware of CAB PrEP as well as with initiation and adherence

4.1.2. Dynamic Implementation

The DI arm will evaluate the feasibility of APRETUDE delivery with implementation supports; specifically determining whether DI results in higher feasibility in delivering APRETUDE. Clinics randomized to DI will receive: 1) enhanced toolkits, 2) a digital health end to end implementation strategy; and 3) implementation facilitation. Figure 2 depicts an example of how these strategies support the CAB PrEP clinical experience and the PrEP care continuum. The description of strategies according to Proctor reporting domains [Proctor, 2013] is presented in Table 2.

Figure 2 Dynamic Implementation Pathway



*Designated injection days will also support retention and transportation will also support PrEP initiation and adherence

- **Enhanced toolkits:** PSPs and relevant site staff, inclusive of SSPs will have access to the standard toolkit items as in the routine implementation arm in addition to enhanced items. Enhanced provider items will include but not limited to a video on using ViiV Connect, training module on providing inclusive care, and a patient-provider decision making tool. Enhanced patient items might include text appointment reminders and videos on what to expect. All items – standard and enhanced - may be available and accessible to site staff and PSPs in a mobile application with web-enabled capabilities. Site staff will receive information and/or training on the patient & provider toolkit items as these items provide product information and education. PSPs could be informed of toolkit information and the mobile application from their clinicians and will be available on the digital platform. Toolkit items will be used as needed.

- **Digital health end to end implementation strategy:** As depicted in Figure 2, digital health end to end implementation strategy supports relevant site staff, inclusive of SSPs, in implementing APRETUDE from identification of APRETUDE eligible individuals to the enrolment, adherence, persistence and retention of PSPs who are on APRETUDE. The Sexual Health Assessment tool may help individuals to self-identify their need for APRETUDE rather than rely solely on clinician identification. The tool is intended to be integrated into standard clinic operations and be a part of routine care offered to all men who seek health services at the site. As such, site staff may integrate the tool into clinic operations and may send the tool digitally to all men seeking care before their clinical visit throughout the study period**.** Any data collected in the tool from men will be collected following agreement to data sharing and privacy; site staff may review the tool results with their patients as part of routine care, which may support site staff in linking men, including MSM and TGM, to PrEP and

prescribing PrEP. Any data reported for study purposes (e.g., shared with Sponsor/ CRO) from the Sexual Health Assessment will be in aggregate form at the site level and be de-identified individual data.

Site staff may develop a plan to make APRETUDE injections accessible by the implementation of designated injection days and a choice of prescheduled appointments and drop-in visits. These options will support PSPs in getting their initial injection and subsequent injections within target windows at times convenient to them. All clinics using the telehealth platform (see Section 4.1.5) will provide a drop-in visit option.

Site staff may provide PSPs with information about transportation available to transport them to their initial and follow-up injection visits, aiding in adherence to target injection windows and retention in care. PSPs requesting transportation will receive digital support to acquire the transportation.

A sub-group of clinics will use a telehealth platform (see Section 4.1.5) to implement CAB PrEP. All the digital strategies will be delivered on the platform and may influence uptake, adherence, retention and persistence on APRETUDE. A sub-group, rather than all DI clinics, will allow for focused iterative feedback and refinement of the platform throughout the study.

- **Implementation Facilitation**: As depicted in Figure 2, implementation facilitation supports the dynamic implementation strategies. The purpose of implementation facilitation is to provide the help and support needed to improve clinical care and patient outcomes through a process of interactive problem-solving within a context of a recognized need for improvement and a supportive interpersonal relationship [Ritchie, 2020]. An external facilitator, an expert in implementation science and knowledgeable of the protocol and the study's implementation strategies, will lead group facilitation calls focused on the exchanging of knowledge, identification of barriers to implementation and identification of solutions to overcome the barriers. The grouping of clinics on the facilitation calls will be determined once sites have been selected; clinics can be grouped by geography, PrEP volume, or another meaningful characteristic that would be helpful for clinics.

  Tailoring implementation strategies to individual settings in the context of applying diverse implementation strategies is important. Individual facilitation can result in effective implementation. SSPs in the DI arm will be offered one-on-one facilitation calls to help problem solve implementation barriers specific to their health facility, including reminding SSPs of the availability of toolkit items that might support them.

  SSPs in the DI arm might participate in quarterly group and monthly one-on-one facilitation calls. Monthly one-on-one calls will not occur in the months the quarterly groups meet. At least one consistent SSP from each site should participate in both one-on-one and quarterly facilitation calls. 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.

Additionally, DI arm clinics will complete the brief monthly FRAME-IS assessments and participate in the study training. All SSPs in the DI arm will be asked to complete the FRAME-IS in order to understand implementation from the perspective of the different roles. SSPs and PSPs will complete all assessments per the SoA (ANNEX 1 and ANNEX 2).

Table 2 Dynamic Arm Implementation Strategies

	Enhanced Toolkits		Implementation Facilitation	Digital Health End to End Implementation			
	Provider Toolkit	**Patient Toolkit**	**Group & 1:1 Calls**	**Sexual Health Assessment**	**Designated Injection Days**	**Transportation Support**	**Telehealth Platform**
Action	Enhanced ViiV connect Materials; inclusive training module and forms; patient-provider decision making tool + RI arm resources	Text/App Reminder, What to Expect Video, Mobile App (with web enabled features)	Interactive group problem solving and one-on-one implementation support	Patients self-assessment of HIV risk and PrEP need.	Clinics have designated injection days, and a choice of prescheduled appointments or drop-in visits	Provision of digital transportation support for patient appointment keeping.	All CAB PrEP clinical services except injection offered through a telehealth platform
Actor	ViiV developed, delivered with IS vendor support	ViiV developed, Clinic staff delivered	IS Vendor	Participants Clinic Staff	Clinic Staff Participants	CRO Clinic Staff Participants	CRO Clinic Staff Participants
Action target	Enhanced resources to improve provider knowledge of CAB PrEP and implementation guidance	Use digital resources to improve participant knowledge about CAB PrEP and support retention in care	Clinics learn best implementation practices in group sessions and clinics overcome implementation barriers in one-on-one sessions	Improve participant identification of HIV risk and linkage to PrEP care and clinician identification of eligible PrEP patients.	Support clinics in providing timely CAB PrEP services for patients to support CAB PrEP initiation, adherence and retention in care.	Support patients in initiating, adhering and retaining in CAB PrEP services.	Understand how best to implement CAB PrEP using telehealth by supporting a sub-group of clinics through the process
Dose	As needed	As needed	Group: quarterly (60-90 mins); 1:1 - monthly (1hr)	Before or at clinical visits	Daily	As needed	Daily, as needed

	Enhanced Toolkits		Implementation Facilitation	Digital Health End to End Implementation			
	Provider Toolkit	**Patient Toolkit**	**Group & 1:1 Calls**	**Sexual Health Assessment**	**Designated Injection Days**	**Transportation Support**	**Telehealth Platform**
Outcome	Feasibility, acceptability, utility	Feasibility, acceptability, utility, adherence	Feasibility, acceptability	Reach, fidelity, feasibility, acceptability	Feasibility, reach, adherence fidelity, acceptability	Acceptability, uptake, adherence, retention, utility	Feasibility, acceptability, uptake, adherence, retention, utility
Justification	Clinicians need added logistic support to integrate new modality into clinics and support working with new population demographics	Patients may benefit from support materials to be aware of CAB PrEP as well as with initiation and adherence delivered via a different modality	Clinics may benefit from best practice sharing while 1:1 support can aid clinics in addressing their unique implementation challenges	Clinicians need to unbiasedly assess patients' eligibility for CAB PrEP and patients need a mechanism to evaluate their own PrEP need.	Clinics may benefit from strategies to reduce care burden but support accessibility and reach to support adherence	Patients may benefit from transportation support to expand accessibility, adherence and retention.	Telehealth may help expand accessibility and reach of PrEP to patients who prefer non-traditional care.

4.1.3. Implementation Assessments

Implementation outcomes align with the study's objectives and Proctor and colleague's [Proctor, 2011] implementation outcome recommendations. The administration of assessments for SSPs and PSPs, including facilitation calls and FRAME-IS, is outlined in Table 3. Baseline assessments should be completed prior to the enrollment of first 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 questionnaires and interviews have been completed.

Table 3 Implementation Assessments

Outcome	Assessment Level	Measurement	OLI/DTI Time point
Feasibility-Overall	Staff Study Participants	FIM	BL, M5, M13
		Staff ISQ	BL, M5, M13
		SSI	M5, M13
	Patient Study Participants	FIM	M13(OLI)/M12(DTI)
		Patient ISQ	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
		SSI	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
Acceptability-Overall	Staff Study Participants	AIM	BL, M5, M13
		SSI	M5, M13
Feasibility - Telehealth	Staff Study Participants	FIM	BL, M5, M13
		SSI	M5, M13
		Staff ISQ	BL, M5, M13
	Patient Study Participants	FIM	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
		SSI	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
		Patient ISQ	BL, M7(OLI)/M6(DTI), M13M13(OLI)/M12(DTI)
Acceptability - Telehealth	Staff Study Participants	AIM	BL, M5, M13
		SSI	M5, M13
		Staff ISQ	BL, M5, M13
	Patient Study Participants	AIM	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
		SSI	BL, M7(OLI)/M6(DTI), M13M13(OLI)/M12(DTI)
		Patient ISQ	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
Acceptability – Cabotegravir LA	Patient Study Participants	AIM	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)

Outcome	Assessment Level	Measurement	OLI/DTI Time point
		SSI	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
		Patient ISQ	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
Fidelity	Patient Study Participants	Adherence to Target date (±7 days), eCRF	Monthly
		Patient ISQ	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
		SSI	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
	Staff Study Participants	Staff ISQ	BL, M5, M13
		SSI	BL, M5, M13
		# clinical staff-initiated assessments/ # eligible pts	Monthly
	Cross Study[1]	Composite measure*: • adherence to target date • assessments given • missed appointments	BL-M13
Reach	Staff Study Participants	# pts receiving 1st injection / #eligible pts based on assessments	Monthly
Awareness	Staff Study Participants	Assessment tool	Monthly
		Staff ISQ	BL, M5
		SSI	BL, M5
	Patient Study Participants	Assessment tool	BL
		Patient ISQ	BL
		SSI	BL
Uptake	Staff Study Participants	Assessment tool	Monthly
		Clinic administrative records	Monthly
		Staff ISQ	BL, M5, M13
	Patient Study Participants	Assessment tool	Monthly
		Patient ISQ	BL
		SSI	BL
Persistence, Retention	Staff Study Participants	Assessment tool	Monthly
		Clinic administrative records	Monthly
		Adherence to Target date (±7 days), admin records	Monthly
		Staff ISQ	BL, M5, M13
	Patient Study Participants	Adherence to Target date (±7 days), eCRF	Monthly
		Patient ISQ	M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
		SSI	M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
Process evaluation of implementation	Staff Study Participants,	SSI	BL, M5, M13

Outcome	Assessment Level	Measurement	OLI/DTI Time point
strategies and toolkits			
	Patient Study Participants	SSI	BL, M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)
Perceptions, barriers & facilitators	Staff Study Participants,	SSI, Staff ISQ	BL, M5, M13
	Patient Study Participants	SSI, Patient ISQ	M7(OLI)/M6(DTI), M13(OLI)/M12(DTI)

Abbreviations: FIM: Feasibility of Intervention Measure; AIM: Acceptability of Intervention Measure; SSI: Semi-Structured Interviews; M: Month; DTI: Direct to Injection; OLI: Optional Oral Lead In
***Composite measure to be developed 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

4.1.3.1. Timepoint Definitions for Completion of Questionnaires and Interviews

PSPs:

- PSPs who are started on oral Cabotegravir PrEP as optional OLI will receive their first dose of oral CAB in Month 1. PSPs who are started on APRETUDE injections (direct to injection) will receive their first dose of APRETUDE injection in Month 1.
- Each administration of APRETUDE injection will be categorized by the sequential number, e.g., Dose 1 visit (first injection), Dose 2 visit (second 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 two weeks of or on their Dose 1 visit and before receiving the first APRETUDE injections.
- For each PSP, the last APRETUDE injection is to occur at the last study visit.
- All study visits, including those where questionnaires and/or interviews are administered at M7(OLI)/M6(DTI) and M13(OLI)/M12(DTI), will be anchored off of each PSP M1, 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.
- Approximately 3 PSPs per site will participate in SSIs; number of SSIs might vary by site. Participants will be purposely sampled for interviews based on demographic characteristics, such as race/ethnicity, prior PrEP use.
- Interviews should be conducted with all PSPs who discontinue participation within one month of discontinuation, when possible.

SSPs:

- Baseline IS assessment is defined as the first assessment taken prior to administering the first APRETUDE injection at each site. Baseline questionnaires should be completed by all SSPs within 1-2 weeks of the site's initiation.
- 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.
    - Questionnaires and/or interviews can be completed within 3 weeks of the respective study visits.
- 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.

Group and 1:1 Facilitation:

- SSPs in the DI arm will meet as a group to actively discuss problem solving for implementation barriers encountered.
    - At least 1 consistent SSP from each site will be required to attend. Sites will be encouraged to send the most knowledgeable and involved individuals in the implementation to the meetings.
    - Group facilitation should occur quarterly, as needed.
- SSPs in the DI arm will be offered one-on-one facilitation calls to help problem solving for individual implementation barriers.
    - At least 1 consistent SSP will participate in the one-on-one calls.
    - One-on-one facilitation calls will be up to monthly as needed except for the months when group facilitation occurs.

FRAME-IS:

- SSPs at each site will complete the FRAME-IS questionnaire each month, which will be sent via email. Additional details on the FRAME-IS are provided in the SRM.

The full SoA can be found in ANNEX 1 and ANNEX 2.

4.1.4. Primary Endpoint

The primary endpoint is Feasibility of Intervention Measure score assessed from SSP Month 13. The secondary implementation endpoints include the feasibility in PSPs, feasibility and acceptability of specific implementation components, reach, fidelity, and utility. Additional secondary measures will assess awareness, uptake, adherence and retention of APRETUDE, adaptations to existing toolkits, and the process of acquiring Cabotegravir. Quantitative and qualitative data as well as facilitation calls and FRAME-IS output will be triangulated to inform final study results.

4.1.5. Telehealth Strategy

Telehealth is a unique strategy within the dynamic implementation arm requiring its own standard operating procedures. Telehealth delivery of APRETUDE is new and is likely to be complex with no similar benchmarks with which to compare. It is important to understand and resolve the known and unknown challenges that may accompany telehealth delivery of APRETUDE before attempting to scale as unresolved challenges can lead to significant opportunity costs. For these reasons, the telehealth strategy will be approached from a developmental evaluation lens, which is an approach that supports continuous adaptation in complex environments, emphasizing iterative, real-time data collection and regular reflection to support adaptation [Fagen, 2011]. Developmental evaluation creates a road map to ensure the right people are reflecting on the right data at the right time to inform changes and that careful, ongoing documentation is occurring in the implementation process.

The approach may provide the foundation for producing the essential information, such as development and design, and optimal strategies for the possible scale-up of telehealth delivery of APRETUDE. The telehealth strategy may be a simulated digital environment or a hybrid system of integrating telehealth components/modules into existing clinic telehealth systems. This will be done in a sub-group of clinics in the study.

Certain functions within the telehealth platform will be made available to potential patients of the PrEP provider as part of routine care and is independent of study participation. Some patients, however, may subsequently become study participants if eligible. Potential patients may take a web-based/online questionnaire, such as the Sexual Health Assessment Tool, that is being implemented as routine care for all men within a clinic. Any questionnaire data collection will only be done following the patient's agreement to consent to data sharing and privacy terms within the platform. Data collected from potential patients will be key coded and reviewed by the provider in order to provide appropriate PrEP care to their patient. Data collected for study purposes (i.e., shared with CRO) will be de-identified in aggregate form only at the site level data is not connected to any individual. Once a patient is linked to a PrEP provider for consideration and provision (including prescribing and administration of APRETUDE injections), then the site staff may consider initiating a discussion around involvement in the study and initiation of study consent discussions. The telehealth strategy may include, but is not limited to:

- Patient web-based/online PrEP questionnaires (e.g. Sexual Health assessment, this does not include the questionnaires noted in the SoA).
- Online appointment scheduling for providers.
- Initial patient-provider interaction through telehealth.
- Provider ability to provide an HIV test or schedule a lab draw (at local lab) during the initial telehealth visit.
- Electronic submission of the HIV test result or result of the lab draw to the PrEP provider.
- Electronic submission of optional oral lead-in prescription from provider (if needed)
- Electronic scheduling of first IM dose for patient from a choice of sites. Potential locations for injection visits at clinic (scheduled or drop-in), or patient home (if allowed).
- Patient benefits verification process (e.g., insurance)
- Home nursing option for home administration (if feasible).
- PSP injection visit scheduling at chosen location.
- Follow-up visits occur with provider via telehealth.

The digital environment developed for this study could be utilized to support future telehealth strategies and designs. Implementation assessments (e.g., facilitation calls, FRAME-IS) may also document the telehealth processes to help inform future scale up. Detail information on the telehealth strategy is given in the SRM.

4.2. Scientific Rationale for Study Design and Research Methods

The HPTN 083 and HPTN 084 studies demonstrated that the efficacy of APRETUDE was statistically superior to daily oral FTC/TDF for PrEP at preventing HIV acquisition in cisgender men who have sex with men and transgender women as well as cisgender women, respectively. Yet, clinical efficacy of a product often does not 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 is 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, APRETUDE 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 APRETUDE 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 in order 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 in order to determine how effectively and efficiently APRETUDE 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.

The study design utilizes unequal randomization ratio of 2:1, whereby twice as many clinics are allocated to the DI arm than the RI arm. Unequal allocation is chosen due to the unequal distribution of implementation resources between the two arms. The DI arm will receive several enhanced supports relative to the RI arm and therefore, unequal allocation is recommended [Dumville, 2006].

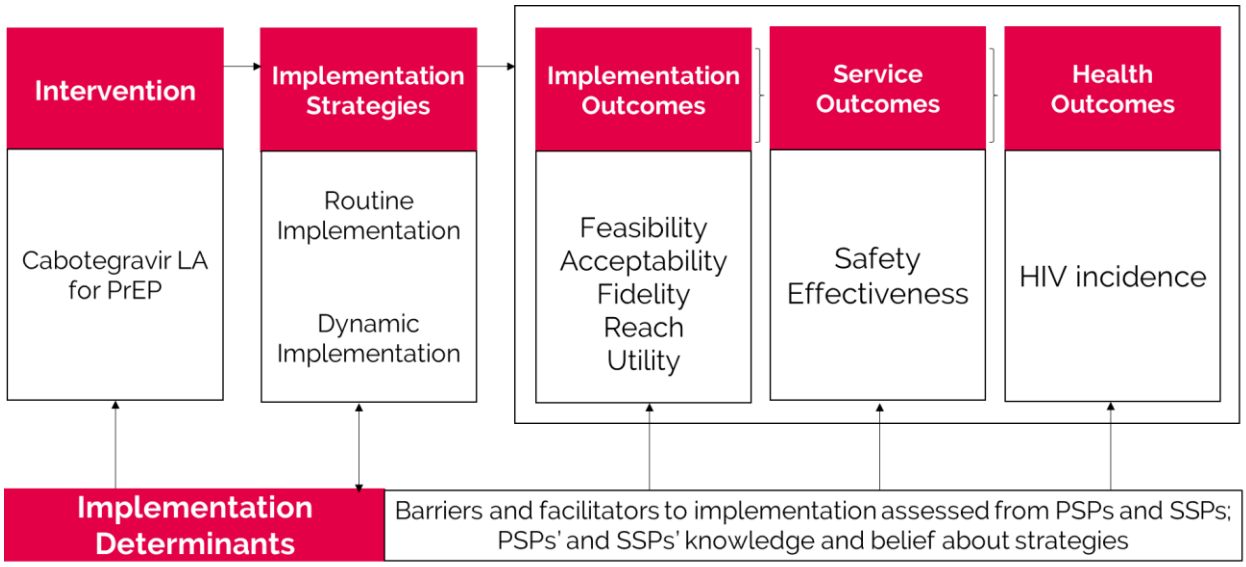
4.2.1. Implementation Frameworks

The study is guided by 3 Gold Standard Implementation Science Frameworks (covering evaluation, determinants, and process): the Proctor [Proctor, 2011] Outcomes Framework, the Consolidated Framework for Implementation Research (CFIR) [Damschroder, 2009] and the Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS) [Miller, 2021].

The Proctor outcomes framework will provide guidance on study design and outcomes [Proctor, 2011]. 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 uninfected) and service outcomes (e.g., on-time APRETUDE 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, utility and reach.

Figure 3 Proctor & CFIR Integration Application



CFIR will be integrated with the Proctor outcomes framework to serve as the process 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. These constructs can be used in a range of applications and for this study, CFIR will be integral to systematically identifying and assessing barriers and facilitators to APRETUDE implementation via the implementation strategies. The framework can be used to develop data collection approaches and therefore, will be used to guide the qualitative interviews with study participants and Study Staff Participants.

Adaptations made to the toolkits, RI and DI will be captured using the FRAME-IS [Miller, 2021]. The FRAME-IS provides a systematic way of documenting and tracking modifications to implementation strategies in traditional healthcare settings, allowing for a better understanding of how the strategies influence outcomes. It is modular, capturing what is modified, the nature of the modification, and the rationale for the modifications. There are also optional modules to capture when modifications occurred, whether they were planned, who participated in the decision making and how widespread they were.

5. Statistical Considerations

The statistical analysis plan will be finalized prior to any interim or final database lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Baseline analyses will be conducted when a sufficient number of SSPs and PSPs complete their baseline assessments. Interim analyses will be conducted when a sufficient number of staff study and/or patient study participant complete study assessments up to the Month 5 time point for SSPs and the Month 7(OLI)/Month 6(DTI) time point for PSPs. Additional interim analysis may be performed as required and will be detailed in the Statistical Analysis Plan (SAP). The purpose of these interim analyses will be to provide early evaluation of the implementation science primary and key secondary objectives.

Completed SSP and PSP questionnaire and interview data collected at the time of the interim data cut, will be included in the analyses. In addition, a limited number of clinical datasets from the eCRF will be included in order to describe the characteristics of the patient study participants enrolled. No formal criteria for stopping or amending the study based on interim analysis results will be made. The SAP will describe the planned analyses in greater detail.

5.1. Statistical Hypotheses

The primary hypothesis on the quantitative aspects of this study is that there is a difference between the dynamic implementation (DI) strategy and the routine implementation (RI) strategy in terms of staff study participants' (SSPs) mean FIM score at Month 13, i.e.,

$$H_{10} : \mu(\text{DI}) = \mu(\text{RI}) \text{ vs } H_{11} : \mu(\text{DI}) \neq \mu(\text{RI}),$$

and the secondary hypothesis is that there is a difference between the dynamic implementation (DI) strategy and the routine implementation (RI) strategy in terms of patient study participants' (PSPs) mean FIM score at Month 13, i.e.,

$$H_{20} : \mu(\text{DI}) = \mu(\text{RI}) \text{ vs } H_{21}: \mu(\text{DI}) \neq \mu(\text{RI}).$$

The two-way ANOVA will be used to test each of the above hypothesis with clinic volume as the stratification factor, where no multiplicity adjustment is planned.

5.2. Study Size

The study is designed to mainly evaluate feasibility and acceptability of some implementation strategies from the feedbacks of SSPs and PSPs using implementation science measures. The study size for SSPs and PSPs will be investigated on the basis of analysis of the standardized effect size

$$d = \frac{\mu(\text{DI}) - \mu(\text{RI})}{\sigma}$$

which is defined as the ratio of difference of mean FIM scores between two arms to the standard deviation σ. To accommodate various scenarios of the mean difference between

arms and the assumed standard deviation, the standardized effect size d is considered without taking into account the effect of ICC (Intra-Cluster Correlation).

Sample Size of SSPs:

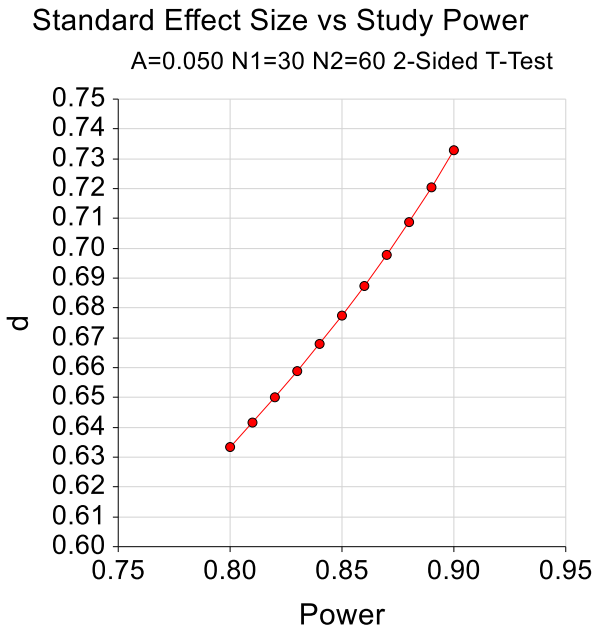
For SSPs, its size consideration consists of two parts: one is based on practical considerations in terms of feasibility of enrolling an adequate number of sites on each implementation strategy with the desire to have interventions tested across two types of study sites (high vs low), and the other is to enroll an adequate number of SSPs in each site to achieve the targeted power to detect the various differences between two arms (DI vs RI) in term of their mean FIM score with the cap 90 on the number of SSPs to be enrolled.

With the cap 90 on the number of SSPs and the allocation of SSPs between DI arm and RI arm being 2:1, the absolute value of d will range approximately from 0.63 to 0.73 if the study power changes from 0.80 to 0.90, as shown in Table 4 below, where Figure 4 illustrates the relationship between d>0 and the study power.

Table 4 Sensitivity of the Absolute Value of Standardized Effect Size to Study Power for SSPs

Power	N1	N2	N	Absolute Value of d
0.8	30	60	90	0.63
0.81	30	60	90	0.64
0.82	30	60	90	0.65
0.83	30	60	90	0.66
0.84	30	60	90	0.67
0.85	30	60	90	0.68
0.86	30	60	90	0.69
0.87	30	60	90	0.7
0.88	30	60	90	0.71
0.89	30	60	90	0.72
0.9	30	60	90	0.73

Figure 4 Relationship between Standardized Effect Size and Study Power for SSPs



Results from study CUSTOMIZE (209493) have shown that the estimated mean score of FIM for SSPs was 4.46 with standard deviation (SD) 0.59 at Month 12. Assuming these results remain valid in our RI arm (N1=30) at Month 13 when 90 SSPs are enrolled in DI and RI with ratio 2:1, to achieve 80% power, the mean score μ(DI) of FIM at Month 13 for DI arm should be at least 4.83 if DI arm behaves better than RI arm, or at most 4.09 if vice versa, as the absolute mean difference $|\mu(DI) - \mu(RI)|$ will be 0.37≈0.59*0.63 (=σ*d). The mean FIM score of DI arm at Month 13 will be at most 4.06 if μ(DI) < μ(RI) or at least 4.86 if μ(DI) > μ(RI) to have 85% power. The other scenarios of μ(DI) are summarized for the range of detectable standardized effect size and the corresponding powers in Table 5.

Table 5 The Mean FIM Score of DI Arm at Month 13 Assuming μ(RI)=4.46 and SD=0.59 for SSPs

Absolute Value of d	Power	μ(DI) if μ(DI) < μ(RI)	μ(DI) if μ(DI) > μ(RI)
0.63	0.8	4.09	4.83
0.64	0.81	4.08	4.84
0.65	0.82	4.08	4.84
0.66	0.83	4.07	4.85
0.67	0.84	4.06	4.86
0.68	0.85	4.06	4.86
0.69	0.86	4.05	4.87
0.7	0.87	4.05	4.87

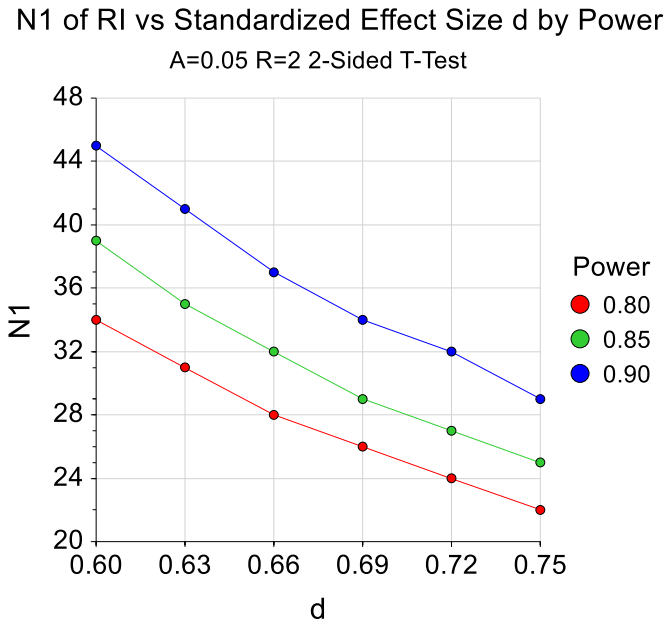
Absolute Value of d	Power	μ(DI) if μ(DI) < μ(RI)	μ(DI) if μ(DI) > μ(RI)
0.71	0.88	4.04	4.88
0.72	0.89	4.04	4.88
0.73	0.9	4.03	4.89

If we consider a series of standardized effect size d, Figure 5 below summarizes the corresponding minimum sample size N1 of RI arm needed to achieve three target powers (80%, 85%, 90%). For the exact sample size of SSPs and their allocation to each arm for d ranging from 0.6 to 0.75, please refer to Table 6. For instance, if we expect the standardized effect size to be 0.66 which is a little larger than 0.63 discussed above, then a total of 84 SSPs is required with 28 in RI arm and 56 in DI arm to achieve 80% power. And approximately 96 SSPs are needed to have 85% power, where 32 SSPs are allocated to RI arm and 64 to DI arm.

Table 6 Sensitivity of Sample Size to Standardized Effect Size for SSPs

d	Target Power	Actual Power	N1 for RI	N2 for DI	Total N
0.6	0.8	0.81	34	68	102
0.6	0.85	0.86	39	78	117
0.6	0.9	0.9	45	90	135
0.63	0.8	0.81	31	62	93
0.63	0.85	0.85	35	70	105
0.63	0.9	0.9	41	82	123
0.66	0.8	0.8	28	56	84
0.66	0.85	0.85	32	64	96
0.66	0.9	0.9	37	74	111
0.69	0.8	0.81	26	52	78
0.69	0.85	0.85	29	58	87
0.69	0.9	0.9	34	68	102
0.72	0.8	0.81	24	48	72
0.72	0.85	0.85	27	54	81
0.72	0.9	0.91	32	64	96
0.75	0.8	0.81	22	44	66
0.75	0.85	0.86	25	50	75
0.75	0.9	0.9	29	58	87

Figure 5 Relationship between Minimum Sample Size Required for RI Arm and the Assumed Standardized Effect Size for SSPs



Sample Size of PSPs:

For PSPs, its sample size will be considered in a similar way to that of SSPs. With the cap 220 on the number of enrolled PSPs and the assumption on the dropout rate about 15% across arms, a series of targeted power will be investigated to determine the number of PSPs needed in each arm that will ensure the detection of the various differences between two arms (DI vs RI) in term of mean FIM score of PSPs at Month 13.

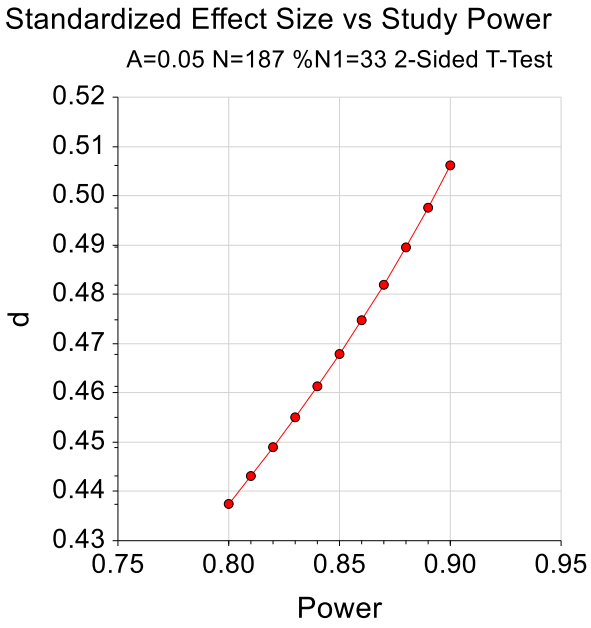
With the dropout rate 15%, at most 187 out of the capped 220 PSPs will remain in both DI arm and RI arm with the ratio 2:1 at Month 13, and the absolute value of standardized effect size d will range from 0.44 to 0.51 when the study power increases from 0.80 to 0.90 as shown in Table 7, where Figure 6 illustrates the relationship between d>0 and the study power.

Table 7 Sensitivity of the Absolute Value of Standardized Effect Size to Study Power for PSPs

Power	N1	N2	N	Absolute Value of d
0.8	62	125	187	0.44
0.81	62	125	187	0.44
0.82	62	125	187	0.45
0.83	62	125	187	0.46
0.84	62	125	187	0.46
0.85	62	125	187	0.47
0.86	62	125	187	0.47

Power	N1	N2	N	Absolute Value of d
0.87	62	125	187	0.48
0.88	62	125	187	0.49
0.89	62	125	187	0.5
0.9	62	125	187	0.51

Figure 6 Relationship between Standardized Effect Size and Study Power for PSPs



Interim Results from study CARISEL (213199) have shown that the estimated mean score of FIM for PSPs in standard arm was 4.7 with standard deviation (SD) 0.49 at Month 4. Assuming these results remain valid in our RI arm at Month 13 when a total of 220 PSPs are enrolled in DI and RI with ratio 2:1, to achieve 80% power, the mean score of FIM at Month 13 for DI arm should be at least 4.92 if DI arm behaves better than RI arm, or at most 4.48 if vice versa, as the absolute mean difference $|\mu(DI) - \mu(RI)|$ will be 0. 22 ≈ 0.49*0.44. The mean FIM score of DI arm at Month 13 will be at most 4.47 if $\mu(DI) < \mu(RI)$ or at least 4.93 if $\mu(DI) > \mu(RI)$ to have 85% power. The other scenarios of $\mu(DI)$ are summarized for the range of detectable standardized effect size and the corresponding powers in Table 8.

Table 8 The Mean FIM Score of DI Arm at Month 13 Assuming μ(RI)=4.7 and SD=0.49 for PSPs

Absolute Value of d	Power	μ(DI) if μ(DI) < μ(RI)	μ(DI) if μ(DI) > μ(RI)
0.44	0.8	4.48	4.92
0.44	0.81	4.48	4.92
0.45	0.82	4.48	4.92
0.46	0.83	4.47	4.93
0.46	0.84	4.47	4.93
0.47	0.85	4.47	4.93
0.47	0.86	4.47	4.93
0.48	0.87	4.46	4.94
0.49	0.88	4.46	4.94
0.5	0.89	4.46	4.95
0.51	0.9	4.45	4.95

If we consider a series of standardized effect size d, Figure 7 below summarizes the corresponding minimum sample size N1 of RI arm needed to achieve three target powers (80%, 85%, 90%). For the exact sample size of PSPs and their allocation to each arm for d ranging from 0.44 to 0.51, please refer to Table 9 below, where N1' is the Dropout-Inflated enrollment sample size for RI arm, N2' is the Dropout-Inflated enrollment sample size for DI arm and N' is the total enrollment sample size for PSPs with dropout rate 15% across arms.

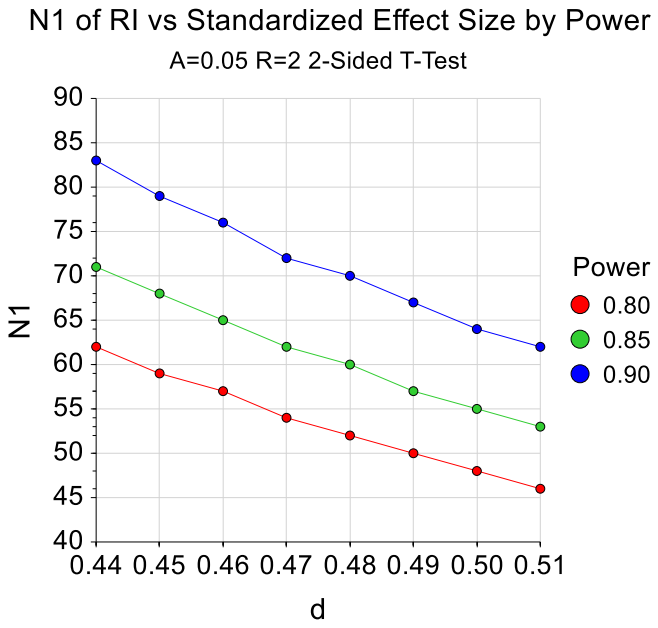
For instance, if we expect the standardized effect size to be 0.45 which is slightly higher than 0.44 discussed above, then a total of 209 PSPs is required to be enrolled with 70 in RI arm and 139 in DI arm to achieve 80% power, while 59 PSPs and 118 PSPs are remained in each arm respectively at Month 13. And approximately 240 PSPs are needed in the enrollment to have 85% power, where 80 PSPs are allocated to RI arm and 160 to DI arm, and 68 PSPs and 136 PSPs are retained in each arm respectively at Month 13.

Table 9 Sensitivity of Sample Size to Standardized Effect Size for PSPs

d	Target Power	Actual Power	N1	N1'	N2	N2'	N	N'
0.44	0.8	0.8	62	73	124	146	186	219
0.44	0.85	0.85	71	84	142	168	213	252
0.44	0.9	0.9	83	98	166	196	249	294
0.45	0.8	0.8	59	70	118	139	177	209
0.45	0.85	0.85	68	80	136	160	204	240
0.45	0.9	0.9	79	93	158	186	237	279
0.46	0.8	0.8	57	68	114	135	171	203
0.46	0.85	0.85	65	77	130	153	195	230
0.46	0.9	0.9	76	90	152	179	228	269
0.47	0.8	0.8	54	64	108	128	162	192

d	Target Power	Actual Power	N1	N1'	N2	N2'	N	N'
0.47	0.85	0.85	62	73	124	146	186	219
0.47	0.9	0.9	72	85	144	170	216	255
0.48	0.8	0.8	52	62	104	123	156	185
0.48	0.85	0.86	60	71	120	142	180	213
0.48	0.9	0.9	70	83	140	165	210	248
0.49	0.8	0.8	50	59	100	118	150	177
0.49	0.85	0.85	57	68	114	135	171	203
0.49	0.9	0.9	67	79	134	158	201	237
0.5	0.8	0.8	48	57	96	113	144	170
0.5	0.85	0.85	55	65	110	130	165	195
0.5	0.9	0.9	64	76	128	151	192	227
0.51	0.8	0.8	46	55	92	109	138	164
0.51	0.85	0.85	53	63	106	125	159	188
0.51	0.9	0.9	62	73	124	146	186	219

Figure 7 Relationship between Minimum Sample Size Required for RI Arm and the Assumed Standardized Effect Size for PSPs



5.3. Essential Analysis

The primary endpoint in terms of feasibility is SSPs' mean FIM score at Month 13 under Dynamic Implementation (DI) arm and Routine Implementation (RI) arm respectively, and the difference of their mean FIM scores between arms. For FIM of SSPs and the difference between arms, descriptive statistics including 95% confidence intervals will be displayed for these estimates. Mean FIM scores will be compared between the two implementation arms to test if the observed difference is statistically significant. In

addition, distribution of FIM items scores will also be compared. P-values will be reported for these comparisons.

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 subject level, the stratification analysis will be performed at the site level to evaluate the impact of the capacity of sites (high volume vs low volume) in responses to two 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 mean FIM scores of SSPs at different timepoints, the change in mean FIM scores from baseline will be analyzed at the designated timepoints. For the specific Telehealth implementation strategy on SSPs, the subgroup analysis on FIM scores including change from baseline will be conducted.

The FIM scores of PSPs will be summarized in the same way as those of SSPs. In addition, subgroup analysis on PSPs will include, but not limited to, factors such as demographic, baseline characteristics, study arm, clinic characteristics and APRETUDE 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.

5.4. Secondary Analysis

Key secondary outcomes include

- Acceptability and feasibility of telehealth delivery: The mean Acceptability of Intervention Measure (AIM) score and Feasibility of Intervention Measure (FIM) score for SSPs and PSPs will be calculated. The scores will be calculated at Baseline, Month 5 and Month 13 for SSPs, and at Baseline, Month 7 (OLI)/Month 6(DTI), and Month 13(OLI)/Month 12(DTI) for PSPs. Change from Baseline of mean score in the AIM and FIM scores at the respective time points from SSPs and PSPs will also be calculated. Descriptive statistics will be used including 95% confidence intervals. Exploratory analyses will be undertaken to assess the variability of responses by factors including but not limited to clinic characteristics, SSP role and study arm.

  Additional analyses will assess SSPs and PSPs responses to acceptability and feasibility questions posed in the IS questionnaires. The finalization of the questionnaires will inform the latter analyses.

Other secondary outcomes to evaluate include:

- Change from baseline in SSPs' FIM score of RI and DI for APRETUDE administration over time

- SSPs perceptions of facilitators and barriers to RI and DI and overall implementation of PrEP into routine care assessed over time
- PSPs mean FIM and AIM score as well as ISQ responses for APRETUDE over time
- Change from baseline in PSPs' AIM score and FIM score as well as ISQ responses for APRETUDE over time
- PSPs perception of facilitators and barriers to feasibility and acceptability of APRETUDE over time`
- SSPs' mean AIM score and ISQ responses for RI and DI for APRETUDE administration over time
- Change from baseline in SSPs' AIM score and ISQ responses for RI and DI for APRETUDE administration over time
- PSPs' mean AIM score and ISQ responses by implementation strategy over time
- Change from baseline in PSPs' mean AIM score and ISQ responses by implementation strategy over time
- Proportion of SSPs and PSPs that agree or completely agree on the ISQ that each implementation strategy is fit for use over time
- SSPs and PSPs perceptions of utility of implementation strategies and PSPs perceptions of facilitators and barriers to acceptability of RI and DI over time
- Proportion of injections occurring within target window from target date (± 7 days for Injection dose 2 and ± 7 days of target date for subsequent injections) over time
- Proportion of PSPs completing target number of injections through M13
- PSPs and SSPs perception of barriers and facilitators to fidelity to injections window over time
- Proportion of site staff who administer Sexual Health Assessment for APRETUDE over time
- Proportion of eligible PSPs for which Sexual Health Assessment for APRETUDE are administered over time
- Proportion of MSM and TGM who take the Sexual Health Assessment over time
- Proportion of MSM & TGM who report having had sex in the last 6 months on Sexual Health Assessment over time
- Proportion of MSM & TGM who expressed interest in PrEP or never heard of PrEP out of those who report having had sex in the last 6 months over time
- Proportion of PSPs who initiate APRETUDE after taking the Sexual Health Assessment over time
- SSPs and PSPs perceptions of Sexual Health Assessment over time

- Summarize components adapted and changes made using FRAME-IS at pre-implementation and over time
- SSPs and PSPs perceptions of barriers and facilitators over time
- Proportion of PSPs with history of PrEP use that complete the Sexual Health Assessment and ISQ and start APRETUDE over time
- PSPs reasons for choosing APRETUDE, including switching, as assessed by SSIs and ISQ
- SSIs, FRAME-IS and facilitation calls assessed qualitatively with SSPs and SSIs with PSPs over time

In general, descriptive summaries will include number of subjects, means, standard deviations, median, first and third quartiles, as well as the minimum and maximum values for continuous outcomes; and counts and proportions are presented for categorical measures for outcomes in endpoints above. Unless otherwise stated, a 95% confidence interval (CI) will be provided for means and proportions.

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 10) [Proctor, 2011, Weiner, 2017, Aarons, 2015]. SSPs analyses will also be conducted by factors including but not limited to study arm, staff role, and clinic characteristics. PSPs analyses will also be conducted by factors including but not limited to study arm, clinic characteristics, APRETUDE initiation method, PrEP use before initiation on CAB PrEP, service delivery method, and patient subgroups if sufficient data are available.

Table 10 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*
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**		

5.5. Other/Tertiary Endpoints

CCI

[redacted]

CCI

[redacted]

CCI

5.6. Qualitative Analyses

Qualitative data collection and analyses for both SSPs and PSPs will be informed by the study frameworks – CFIR and Proctor outcomes framework. SSPs and PSPs perceptions on implementation, including but not limited to facilitators and barriers, implementation of PrEP into routine care, quality of care, will be assessed by semi-structured qualitative interviews, implementation science questionnaire, FRAME-IS, implementation monitoring calls and facilitation calls. The qualitative data are embedded within the quantitative outcomes of the study for expansion and triangulation of data. All qualitative data will be recorded, transcribed, translated if necessary, cleaned. Data will be entered into a qualitative data management software and any notes from calls will be compiled and analyzed. The Implementation Science vendor will be responsible for coding all qualitative assessments for use in the evaluation of the study outcomes. Established procedures to enhance validity will be used, including development of an audit trail documenting analytical decisions, agreeing on a threshold for rater agreement, and documenting coding decisions.

The goals, objectives and key research questions will guide all aspects of the qualitative analyses. Using content analysis, analytical categories to describe and explain observations will be identified. Codes will be derived deductively by identifying categories at the beginning of the research using the study framework and interview guides as well as inductively by identifying those that emerge gradually from the data. Operational definitions of each code will be used and through constant comparison, updates to the coding model will occur throughout to support efforts to index the data and

lead to further refinement. Qualitative and quantitative data may be integrated for expansion, development, and convergence to assist in the understanding of processes and characteristics that may influence implementation outcomes of APRETUDE.

5.7. Limitations of the Research Methods

The two arms are randomized with ration 2:1 on the site level, which leads to the unbalance of subjects under different interventions. This might reduce the study power with a fixed sample size.

6. Protection of Human Subjects

6.1. Ethical Approval and Participant 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 study participants.

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 study participants.

The PrEP Provider 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.

6.2. Participant Confidentiality

6.2.1. 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.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, in order to meet the study objectives and to determine if the trial participants are truly representative of the impacted population.

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.

6.2.2. 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.

6.3. Informed Consent Process

The PrEP Provider or his/her representative will explain the nature of the study, including the risks and benefits, to the participant, or their legally authorized representative and answer all questions regarding the study.

- Potential PSPs must be informed that their participation is voluntary. PSPs will be required to physically or electronically 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 physical or electronic informed consent was obtained before the participant was enrolled in the study and the date the physical or electronic consent was obtained. The study site authorized person obtaining the informed consent must also sign the ICF.
- PSPs must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A physical or electronic copy of the ICF(s) must be provided to the participant or their legally authorized representative.

The Sponsor (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 Cabotegravir 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 PrEP Provider 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. 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 ViiV Healthcare. No dose reductions, modifications, or changes in the frequency of any components of CAB PrEP, i.e., 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 [APRETUDE, 2021].

7.1. 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 the USPI.**

Any changes in a PSP's CAB PrEP 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) [APRETUDE, 2021]. PrEP providers should refer to the USPI [APRETUDE, 2021] and CDC PrEP guidelines [Centers for Disease Control and Prevention, 2021] for the appropriate management of incident HIV infection (i.e., HIV infection identified following start of CAB PrEP).

7.2. Treatment of an Overdose

For this study, any dose of CAB PrEP greater than listed in the USPI will be considered an overdose [APRETUDE, 2021]. 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 [APRETUDE, 2021].
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

7.3. 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 [APRETUDE, 2021].

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 CAB PrEP USPI must be recorded in the eCRF at each visit [APRETUDE, 2021].

8. Discontinuation of CAB PrEP and Participant Discontinuations

8.1. 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 [World Health Organization, 2020].

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

8.2. 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, i.e., if CAB PrEP is permanently discontinued, then such PSP will no longer be eligible to continue the study.

8.3. 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) 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.

A 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. If the SSP is retaining the role, reasons for withdrawal will be ascertained.

8.4. 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 is 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.
- Should the PSP continue to be unreachable, 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. Else, an SSP who leaves their role will be replaced with the SSP who assumes the role to complete subsequent assessments.

9. 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 (See Section 9.1.).

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 9.3.5.

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 9.1).

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.

9.1. 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 [APRETUDE, 2021].

Adverse events that occur during the trial should be evaluated by the PrEP provider 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 the CRO..
- AEs/Adverse drug reactions (ADRs) reported at the Baseline/Month 1 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 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 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.

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

- AEs that meet the criteria for documentation listed in Section 9.1, and all SAEs will be collected from the signing of the informed consent form until the PSP completes or withdraws from the study, at the timepoints specified in the SoA (ANNEX 1 and 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 and 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.

- A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined earlier in this Section 9.1.1.

- 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, the PrEP Provider must record it in the medical records. If the PrEP Provider considers the event to be reasonably related to the study intervention or study participation, the PrEP Provider must promptly notify the sponsor.

9.1.2. 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.

9.1.3. 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 8.4). Further information on follow-up procedures is given in the SRM.

9.1.4. Regulatory Reporting Requirements for SAEs

The definition of serious adverse events (SAEs) can be found in ANNEX 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.

9.2. Safety Assessments

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

9.2.1. Clinical safety laboratory assessments

Local 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 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 [Centers for Disease Control and Prevention, 2021].

9.2.2. Liver Chemistry Monitoring

The decision whether to discontinue CAB PrEP in the presence of abnormal liver tests should be made by the PrEP provider in accordance with the PrEP CDC clinical management guidelines [Centers for Disease Control and Prevention, 2021] and the US prescribing information for CAB tablet for PrEP and APRETUDE [APRETUDE, 2021]

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.Section 9.2.1

9.3. 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.

9.3.1. 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 Division of AIDS (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.

9.3.1.1. 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.

9.3.1.2. 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 Sponsor or designee as described in ANNEX 4.

9.3.2. 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 Section 9.1.1 will require reporting within 3 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 to the sponsor 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.

9.3.3. 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 the 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.

Whilst pregnancies are not part of the study **they will be reported to the Sponsor or designee within 24 hours of awareness and documented in the eCRF**. All pregnancies will be followed up until outcome (including premature terminations and complications) for both mother and child.

The PrEP Provider will be provided with 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 Antiretroviral Pregnancy Registry (APR) by the Sponsor. The PrEP Provider must not report to APR, to avoid duplication.

The pregnancy must be followed up to determine 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. 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 the 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 SRM for details). While the PrEP Provider is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- The Sponsor's central safety department will also forward this information to the Antiretroviral Pregnancy Registry. The international registry 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.

9.3.4. 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 sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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.

9.3.5. 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.

9.3.5.1. 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.

9.3.5.2. 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.

9.3.5.3. 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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11. ANNEX

11.1. ANNEX 1: Schedule of Activities – Direct to injection

Procedure[1]	**Screening/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **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. All other screening/eligibility procedures (excluding informed consent) should only be performed after receiving this benefits 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 HCV 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 3.3.1 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 the D1 visit: 1) complete questionnaires and assessments prior to or at the visit, and 2) Receive first intramuscular (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/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **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 assessed during screening.
Benefits verification, as needed	X														
Demography	X														
Medical History	X														
Current Medical Conditions	X														

Procedure[1]	**Screening/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Laboratory assessments	X – needed at BL, M6 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 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.
Study Treatment: Participants who are started on oral CAB PrEP as optional oral lead in will receive their first dose of oral CAB on M1. Participants who are started on APRETUDE injections (direct to injection) will receive their first dose of APRETUDE injection on M1. **All injections will be administered according to the** APRETUDE **USPI.**															
Cabotegravir LA PrEP IM Initiation injection		X													

Procedure[1]	**Screening/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **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 drug-drug interaction (DDI) per the CAB tablet for PrEP or APRETUDE USPI;

Procedure[1]	**Screening/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **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 status	X	←==========→												X	Ask person of childbearing potential at each visit if they are pregnant and ask for the date of their LMP.
Questionnaires and Interviews: Questionnaires and Interviews should be completed before receiving APRETUDE IM injections															

Procedure[1]	**Screening/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Patient Study Participants PSP baseline questionnaires should be completed within two weeks prior to or on their D1 visit and before receiving the 1st APRETUDE injection. Participants interviews should be completed within two weeks prior to or two weeks following their D1 visit and within two weeks prior to or two weeks following the target dates for their D4 and D7 visits. Approximately 3 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 race/ethnicity, prior PrEP use. All additional study visits, including those where questionnaires and/or interviews are administered at M6 and M12, will be anchored off of each participants M1 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.															
PSP Questionnaires		X					X						X	X	To be completed prior to injection.
Participant Interviews		X					X						X	X	Interviews will be completed on a subset of PSPs (see Section 4.1.3.1). Window within 2 weeks before or 2 weeks following study visit.

Procedure[1]	**Screening/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Staff Study Participants: Month 1 questionnaires should be completed prior to the first participant is enrolled 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 site initiation. For sites with both OLI and DTI participants, M4/M5 visit will be defined by the target date 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 by the target date when 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. Interim and final SSP questionnaires and/or interviews can be completed within 3 weeks prior to or 3 weeks after study visits. Implementation facilitation, implementation monitoring, and FRAME-IS can begin after baseline questionnaires have been completed by all SSPs. Sexual Health Assessment and aggregate clinic PrEP-related data collection can start prior to participant enrolment.															
SSP Questionnaires	X				X								X	X	At least 1 participant must include an SSP who prescribes APRETUDE.
SSP Interviews					X								X	X	

Procedure[1]	**Screening/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Implementation Facilitation Calls (DI Arm Only)		X	X	X	X	X	X	X	X	X	X	X	X		Group - Quarterly: At least 1 consistent SSP knowledgeable of implementation. One-on-one - monthly: At least 1 consistent SSP knowledgeable of implementation.
Implementation Monitoring (RI Arm Only)		X	X	X	X	X	X	X	X	X	X	X	X		At least 1 consistent SSP knowledgeable of implementation to participate.
FRAME-IS Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X		All SSPs in the RI and DI arms will be asked to complete.
Sexual Health Assessment (DI Arm Only)	X	X	X	X	X	X	X	X	X	X	X	X	X		

Procedure[1]	**Screening/ Enrollment Up to 90 days**[2]	**Treatment Period**[4] Month(M)/Dose(D)												**E.D.**[5]	**Notes**
		M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**		
		D1[3] **visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Site level PrEP Information Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X		Quarterly aggregate clinic PrEP-related data.

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

Procedure[1]	**Screening/ Eligibility/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**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. All other screening/eligibility procedures (except informed consent) should only be performed after receiving this benefits 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 HCV 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 3.3.1 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 for the D1 visit: 1) complete questionnaires and assessments prior to or at the visit, and 2) Receive first intramuscular (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/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**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 procedures as outlined in this protocol.
Inclusion and exclusion criteria	X															Inclusion/exclusion criteria will be fully assessed at the enrolment/ D1 Visit.
Benefits verification, as needed	X															
Demography	X															

Procedure[1]	**Screening/ Eligibility/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**OLI**	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Medical History	X															
Current Medical Conditions	X															
Laboratory assessments	X	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 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 (viral load, genotype/phenotype, recency assay) 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.
Study Treatment: Participants who are started on oral Cabotegravir PrEP as optional oral lead in will receive their first dose of oral CAB in M1. Participants who are started on APRETUDE injections (direct to injection) will receive their first dose of APRETUDE injection in M1. **All injections will be administered according to the CAB LA for PrEP USPI.**																
CAB tablets for PrEP		X														

Procedure[1]	**Screening/ Eligibility/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**OLI**	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
CAB LA for PrEP IM Initiation injection			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.
CAB LA for 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.

Procedure[1]	**Screening/ Eligibility/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**OLI**	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Concomitant medication review	X	←==========→													X	Contraindicated or concomitant medications with the potential for drug interactions according to the CAB PrEP USPI only must be recorded in the eCRF at each 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.

Procedure[1]	**Screening/ Eligibility/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**OLI**	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Pregnancy status	X	←==========→													X	Ask person of childbearing potential at each visit if they are pregnant and ask for the date of their LMP.
Questionnaires and Interviews: Questionnaires and Interviews should be completed before receiving APRETUDE IM injections																
Patient Study Participants PSP baseline questionnaires should be completed within two weeks prior to or on their D1 visit and before receiving the 1st CAB LA for PrEP injection. Participants interviews should be completed within two weeks prior to or two weeks following their D1 visit and within two weeks prior to or two weeks following the target dates for their D4 and D7 visits. Approximately 3 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 race/ethnicity, prior PrEP use. All study visits, including those where questionnaires and/or interviews are administered at M7 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.																
Participant Questionnaires			X					X						X	X	To be completed prior to injection.

Procedure[1]	**Screening/ Eligibility/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**OLI**	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Participant Interviews			X					X						X	X	Interviews will be completed on a subset of PSPs (see Section 4.1.3.1). Window - within 2 weeks before or 2 weeks following the indicated study visit.

Staff Study Participants: Month 1 questionnaires should be completed prior to the first participant is enrolled

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 site initiation.

For sites with both OLI and DTI participants, M4/M5 visit will be defined by the target date 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 by the target date when 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 OLI participants, the visits will be defined at M5 and M13, respectively. If a site has only OLI patients, the SSP assessment follows the OLI SOA in ANNEX 1.

Interim and final SSPs questionnaires and/or interviews can be completed within 3 weeks prior to or three weeks after study visits.

Implementation facilitation, implementation monitoring, and FRAME-IS can begin after baseline questionnaires have been completed by all SSPs. Sexual Health Assessment and aggregate clinic PrEP-related data collection can start prior to participant enrolment.

Procedure[1]	**Screening/ Eligibility/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**OLI**	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
SSP Questionnaires	X					X								X	X	At least 1 participant must include an SSP who prescribes APRETUDE.
SSP Interviews						X								X	X	
Implementation Facilitation Calls (DI Arm Only)			X	X	X	X	X	X	X	X	X	X	X	X		Group Quarterly: At least 1 consistent SSP knowledgeable of implementation. One-on-one - monthly: At least 1 consistent SSP knowledgeable of implementation.
Implementation Monitoring (RI Arm Only)			X	X	X	X	X	X	X	X	X	X	X	X		At least 1 consistent SSP knowledgeable of implementation participate
FRAME-IS Questionnaire			X	X	X	X	X	X	X	X	X	X	X	x		All SSPs in the RI and DI arms will be asked to complete.

Procedure[1]	**Screening/ Eligibility/ Enrollment**[2]	**Treatment Period**[4] Months (M) & Dose (D)													**E.D.**[5]	**Notes**
		M1 (At least 28 days)	**M2**[3]	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**		
	Up to 90 days	**OLI**	**D1 visit**	**D2 visit**		**D3 visit**		**D4 visit**		**D5 visit**		**D6 visit**		**D7 visit**		
Sexual Health Assessment (DI Arm Only)	X	X	X	X	X	X	X	X	X	X	X	X	X	x		
Site level PrEP Information Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	x		Quarterly aggregate clinic PrEP-related data.

11.3. ANNEX 3. List of Stand-Alone Documents

Study Reference Manual (SRM)

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

11.4.1. 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 local [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.

11.4.2. 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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o 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.

11.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
PrEP Providers 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

11.4.4. 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 the Sponsor in lieu of completion of the Sponsor required form. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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 the Sponsor. • 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 make an assessment of 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 the Sponsor. However, **it is very important that the PrEP Provider always make an assessment of**

Assessment of Causality
causality for every event before the initial transmission of the SAE data to the Sponsor**.** • The PrEP Provider may change his/her opinion of causality in light of 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 the Sponsor 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 the Sponsor with a copy of any postmortem 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 the Sponsor within 24 hours of receipt of the information.

11.4.5. Reporting of SAE to the Sponsor

SAE Reporting to the Sponsor via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to the Sponsor 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.

SAE Reporting to the Sponsor via Electronic Data Collection Tool
• If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to the Sponsor 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.

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

11.5.1. 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.

11.5.2. Reporting of Medical Device Deficiencies

• **Reporting to the Sponsor**
• 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 the CRO and Sponsor.

11.6. 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.

11.6.1. 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, questionnaires, 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 PrEP Provider 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 PrEP Provider of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-PrEP Provider. Any such changes should be documented in the site's source records. Any permanent changes in a PrEP Provider should be communicated to the sponsor.
- There may also be circumstances where immediate actions are required by the sponsor and/or PrEP Provider, outside of what is contemplated in the protocol, in order 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.

11.6.2. 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 PrEP Provider, or the PrEP Provider 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.

11.6.3. COVID-19 Specific Data Capture

11.6.3.1. 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.

11.6.3.2. 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. PrEP Providers 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, PrEP Providers 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.

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

11.7.1. Financial Disclosure

PrEP Providers and sub-PrEP Providers 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. PrEP Providers are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.7.2. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, a PrEP Provider signatory will be identified for the approval of the clinical study report. The PrEP Provider 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 Sponsor site or other mutually agreeable location.
- The Sponsor will also provide all PrEP Providers who participated in the study with a summary of the study results and will tell the PrEP Providers what treatment their patients received. The PrEP Provider(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, The Sponsor intends to make anonymized participant-level clinical and implementation science 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 study participants 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 the Sponsor's Policy.
- The Sponsor 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 study participants 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.

11.7.3. 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 PrEP Provider 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 PrEP Provider 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 PrEP Provider 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 PrEP Provider 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.

11.7.4. 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 PrEP Provider'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 PrEP Provider 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 PrEP Provider 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.

11.7.5. 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 center initiated (first site open) and will be the study start date.

Study/Site Termination

The Sponsor 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 The Sponsor. 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 PrEP Provider 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 PrEP Provider may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the PrEP Provider 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 PrEP Provider
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the PrEP Providers, 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 PrEP Provider shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

11.7.6. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the PrEP Provider 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 multicenter studies only in their entirety and not as individual site data. In this case, a coordinating PrEP Provider 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.

11.8. ANNEX 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment [1]: 18-FEB-2022

This amendment was considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European.

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

Minor editorial changes for accuracy, clarity, formatting and consistency have been made throughout the document and are not included in the description(s) below

Bold: Newly added text

Section # and Name	Description of Change	Brief Rationale
Abstract	Used to read: CAB LA for PrEP will provide people who are at higher risk of HIV acquisition with a new prevention option. Now reads: CAB LA for PrEP **(hereafter referred to as APRETUDE)** will provide people who are at higher risk of HIV acquisition with a new prevention option.	Update the terminology from CAB LA for PrEP to APRETUDE throughout the protocol. With the FDA approval of APRETUDE in Dec 2021, it is important that the terminology was aligned with what a participant would readily identify in the real world.
ANNEX 1 and 2: Schedule of Activities – direct to inject**ion**/Oral Lead In (Section 11.1 and 11.2)	Updates to the schedules of activity (SoAs) to align with the USPI in Annex 1 and Annex 2 and changes in the protocol.	Providers are advised to follow the APRETUDE USPI for the preparation and administration of the product. The SoAs were updated to align with the USPI to avoid any confusion with the study sites.

Section # and Name	Description of Change	Brief Rationale
		The SoAs were also updated to reflect the changes made throughout the protocol.
Study Design Schematic (Section 3.1)	Figure 1. Study Schema updated	Schema updated to reflect updated screening and enrolment period of up to 90 days and updated months (due to alignment with SoAs)
Study Design (Section 3.1)	Used to read: The period includes up to a 21-day screening period and a Now reads: **The study includes a screening period of up to a 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.**	Updated to reflect changes in screening and enrollment period.
Study Population (Section 3.2)	Used to read: And at least five SSPs per site will be included. Now reads: **The number of SSPs will vary by site and approximately 5 per site will be included.**	Clarification on SSPs.
Abstract/ Objectives and endpoints (Section 2)	Changed terminology from PrEP Needs Assessment to **Sexual Health Assessment** and revised the endpoints	Feedback from the community advised that the language 'PrEP Needs

Section # and Name	Description of Change	Brief Rationale
Secondary Analysis (Section 5.4)	associated with the Sexual Health Assessment **Added endpoint:** **SSPs and PSPs perceptions of Sexual Health Assessment over time**	Assessment' might be stigmatizing.
Secondary Analyses (Section 5.4)	Added: **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** Added: **Table 10**	A table and text was added to clearly outline the definitions of implementation outcomes and additional terminology use to measure them that are used in the implementation science questionnaires.
Objectives and Endpoints (Section 2) Secondary Analysis (Section 5.4)	To evaluate fidelity and reach of client Sexual Health Assessments for APRETUDE Two endpoints were added: 1) **Proportion of MSM & TGM who report having had sex in the last 6 months through M13 on the Sexual Health Assessment by service delivery method;** 2) **Proportion of MSM & TGM who expressed interest in PrEP or never heard of PrEP out of those who report having had sex in the last 6 months**	Endpoints added to reflect data will measure fidelity and reach. Clarifying text was added.

Section # and Name	Description of Change	Brief Rationale
	through M13 by service delivery method. Additional text added to endpoint: **by clinic characteristics, patient subgroups, and service delivery method (e.g., telehealth vs. face-to-face in clinic)**	
Objectives and Endpoints (Section 2) Secondary Analysis (Section 5.4)	To evaluate fidelity to injection and dosing window One endpoint was added: **Proportion of PSPs completing target number of injections through M13 and by patient subgroups**	Endpoints added to reflect data that will measure fidelity.
Objectives and Endpoints (Section 2/ Section 5.4)	Timepoints updated throughout endpoints and throughout protocol: Used to read M4 M12 M6/M5 M12/M11 Now reads: **M5** **M13** **M7(OLI)/M6(DTI)** **M13(OLI)/M12(DTI)**	Changes to timepoints to align with SoAs.

Section # and Name	Description of Change	Brief Rationale
Objectives and Endpoints (Section 2) Other/tertiary Endpoints Section 5.5)	To evaluate the PrEP continuum of care at site-level Removed endpoints Added one endpoint: CCI [redacted]	Endpoints adjusted based on the data that will be available during the trial.
Objectives and Endpoints (Section 2) Other/tertiary Endpoints Section 5.5)	To evaluate feasibility of implementation of APRETUDE Updated text to endpoint: CCI [redacted]	Endpoints updated to reflect data that will measure feasibility.
Objectives and Endpoints (Section 2) Other/tertiary Endpoints Section 5.5)	Added a tertiary objective and endpoint focused on CCI [redacted] CCI [redacted]	CCI [redacted]
Objectives and Endpoints (Section 2)	To evaluate perceptions, barriers and facilitators with SSPs and PSPs'	Upon review of the implementation science questions, several key

Section # and Name	Description of Change	Brief Rationale
Secondary Analysis Section 5.4)/Abstract	Moved the endpoint from tertiary to secondary: SSIs, FRAME-IS and facilitation calls assessed qualitatively with SSPs and SSIs with PSPs over time	questions are included under this endpoint.
Objectives and Endpoints (Section 2) Secondary Analysis Section 5.4)	To evaluate switch from oral PrEP to APRETUDE Edited endpoint: PSPs reasons for choosing **APRETUDE**, including switching, as assessed by **SSIs and ISQ**	Clarification
Objectives and Endpoints (Section 2) Secondary Analysis (Section 5.4)	Added acronyms for implementation science questionnaire and implementation monitoring calls ISQ=implementation science questionnaire IMC= implementation monitoring calls	Added the acronyms for clarity in noting the set of Implementation Science questionnaires being administered in the study. The ISQ and IMC themselves are not new questionnaires.
Objectives and Endpoints (Section 2)/Secondary Analysis (Section 5.4)	Added footnote: **If the site has only DTI patients, endpoints will be a month prior for SSPs.**	Clarification of DTI schedule
SSPs (Section 3.3.2)	Added clarification on when baseline questions for SSPs will be completed: 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**	Clarification

Section # and Name	Description of Change	Brief Rationale
	started CAB PrEP with or without optional OLI. Added clarification of documentation in the eCRF: 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).**	
Implementation Assessments (4.1.3)	Updates to Table 3	Changes to nomenclatures for timepoints and updated acronyms
Timepoints Definitions for Completion of Questionnaires and Interviews (4.1.3.1)	Added: **Approximately 3 PSPs per site will participate in SSIs; number of SSIs might vary by site.** Participants will be purposely sampled for interviews based on demographic characteristics, such as race/ethnicity, prior PrEP use. Edited and added: **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**	Clarification Clarification

Section # and Name	Description of Change	Brief Rationale
	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. Questionnaires and/or interviews can be completed within 3 weeks of the respective study visits. **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.** Removed: or OLI PSPs; Dose 1 (first oral dose), Dose 2 (first injection) Added text: **at least 1 consistent SSP will participate in group and 1:1 facilitation**	Clarification Clarification
Routine Implementation (4.1.1.)	Added: **All SSPs will be asked to complete the FRAME-IS in order to understand implementation from the perspective of the different roles.** **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	Clarified the roles participating in the implementation assessments and the approximate number of participants. Clarified the SSP roles who will complete implementation assessments and the PSPs who will be interviewed.

Section # and Name	Description of Change	Brief Rationale
	out on behalf of the clinic and communicate back to the team at the clinic.	
Dynamic Implementation Pathway (Section 4.1.2)	Updated Figure 2: Dynamic Implementation Pathway Clarification of site staff training, sharing of data with Sponsor, and de-identified data. Added: **At least one consistent SSP from each site should participate in both one-on-one and quarterly facilitation calls.** 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. Added: **All SSPs in the DI arm will be asked to complete the FRAME-IS in order to understand implementation from the perspective of the different roles.**	The figure was updated to change the language from PrEP Needs Assessment to Sexual Health Assessment Clarification Clarification on data collection Clarification on data collection
Statistical Considerations (Section 5)	Added: **Baseline analyses will be completed when a sufficient number of staff study participants complete their baseline assessments.**	The protocol did not previously specify when baseline analyses will be completed

Section # and Name	Description of Change	Brief Rationale
	Month 5-time point for SSPs **Month 7(OLI)/6(DTI) time point** Time points are revised from M12 **to M13**	Added and/or clarified timepoints based on updates made in SOAs.
Exclusion Criteria for SSPs (3.2.1.4.)	Used to read: Engaged or planned engagement in an implementation science study on long acting injectables at any time during the study. Now reads: Engaged or planned engagement in an implementation science study with **similar strategies** on long acting **PrEP** injectables at any time during the study.	The intent of the previous criteria was not clear and could negatively impact a site's engagement in research in other therapeutic areas. Therefore, additional clarity was added to the exclusion criteria.
Pregnancy (Section 9.3.3)	Use to read: If a pregnancy is reported, the site will record pregnancy information on the appropriate form and submit it to Syneos (CRO) within 24 hours of learning of the pregnancy and should follow the procedure outlined in SRM. Now reads: If a pregnancy is reported, the site will record pregnancy information on the appropriate form and submit it to **the Sponsor**	Pregnancy reporting guidance was updated based on updated safety guidance in the FDA approved Apretude USPI Dec 2021.

Section # and Name	Description of Change	Brief Rationale
	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.** **Clarification of text:** Whilst pregnancies are not part of the study, **they will be reported to the sponsor or designee within 24 hours of awareness and documented in the eCRF**	
Reporting of AEs and timelines (Section 9.3.2)	Used to read: All SAEs need to be reported within 24 hours of documentation sent by an automated, electronic safety alert within the CRF, All AEs listed below will require reporting within 3 days. **Now reads:** **All SAEs will be recorded and reported immediately and under no circumstance should this exceed 24 hours., All AEs listed in Section 9.1.1 will require reporting within 3 days**	Clarified the reporting of AEs.
Liver Chemistry Monitoring (Section 9.2.2)	Used to read: The decision whether to discontinue CAB PrEP in the presence of abnormal liver tests should be made	Information was updated to reflect the safety guidance in the FDA approved Apretude USPI Dec 2021

Section # and Name	Description of Change	Brief Rationale
	by the PrEP provider in accordance with the PrEP CDC clinical management guidelines and the US prescribing information for CAB tablet for PrEP and CAB LA for PrEP 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. The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in ANNEX 4. Now reads: The decision whether to discontinue CAB PrEP in the presence of abnormal liver tests should be made by the PrEP provider in accordance with the PrEP CDC clinical management guidelines and the US prescribing information for CAB tablet for PrEP and **APRETUDE.** **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**	

Section # and Name	Description of Change	Brief Rationale
	and should be completed in a timely manner.	
References (Section 10)	Added reference for the CDC guidelines published in 2021 and linked the references accordingly where cited in the protocol. Added references for Weiner and Aarons and linked the references accordingly where cited in the protocol	Added reference that was not available at the time of the original protocol. Added references to new content in the protocol
Annex 1 (Section 11.1) Annex 1 (Section 11.2)	Used to read: The screening period will be up to 21 days. Screening/enrollment can occur on the same date as the first Cabotegravir LA for PrEP injection as long as a negative HIV test is documented within the prior 7 days and prior to initiation of CAB LA for PrEP. During screening/enrollment, the following will be completed for PSPs: 1) Informed consent form (ICF), 2) Confirm Inclusion and Exclusion criteria, 3) demography 4) Medical History, including history of HCV infection, and Current medical conditions 5) required labs per clinical local standard of care. It will be completed and a negative HIV test needs to be documented for eligible PSPs within the prior 7 days	Updated to reflect changes in screening and enrollment period

Section # and Name	Description of Change	Brief Rationale
	to initiation of CAB LA for PrEP. Now reads: **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 HCV 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**	

Section # and Name	Description of Change	Brief Rationale
	is documented within 7 days prior to initiation of APRETUDE. Refer to Section 3.3.1 for details on re-screening for PSPs who fail screening. Added: **Approximately 3 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 race/ethnicity, prior PrEP use. Added: Contraindicated or concomitant medications with the potential for drug interactions according to the CAB PrEP USPI only must be recorded in the eCRF at each visit. Added: **To be completed prior to injection.** Added: **All SSPs in the RI and DI arms will be asked to complete.** Added: **At least 1 consistent SSP knowledgeable of**	Clarification Clarification Clarification Clarification Clarification

Section # and Name	Description of Change	Brief Rationale
	implementation to participate. Added: **Site level PrEP Information Questionnaire** Added: **Quarterly aggregate clinic PrEP-related** Added: **One-on-one - monthly: At least 1 consistent SSP knowledgeable of implementation.** Added: **Group - Quarterly: At least 1 consistent SSP knowledgeable of implementation.** Added: **At least 1 participant must include an SSP who prescribes APRETUDE.** Added: **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**	Clarification Clarification Clarification Clarification Clarification

Section # and Name	Description of Change	Brief Rationale
	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.** Added: **Interviews will be completed on a subset of PSPs (see Section 4.1.3.1). Window within 2 weeks before or 2 weeks following study visit.** Updated enrollment days and months Changed Day 1 to Month 1 Added row for benefits verification	Clarification Revisions based on new enrollment period Revisions based on USPI Revisions based on changes to enrollment
List of Abbreviations	DTI = direct to injection VHC = ViiV Healthcare	Added explanation of acronym previously used in protocol to the list of abbreviations

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 13-Apr-2023 09:08:25 GMT+0000

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