CAB-RPV LA Implementation Strategies among High-Risk Populations
Objective 2 Protocol – Revised

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List of Abbreviations

Abbreviation	Abbreviation definition
PT	Project Trust
CAB-RPV LA	Cabotegravir-Rilpivrine Long Acting
ART	Antiretroviral Treatment
PLWH	People Living with HIV
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance Framework
i-PARIHS	Integrated Promoting Action on Research Implementation in Health Services Framework
BMC	Boston Medical Center
CID	Boston Medical Center Infectious Disease Clinic (HIV clinic)
ARCH	Active Retention in Care in Health
CBO	Community-Based Organization
EHR	Electronic Health Record
MRN	Medical Record Number
ITT	Intention to Treat
BUMC	Boston University Medical Campus

Protocol Summary

Title:	CAB-RPV LA Implementation Strategies for High-Risk Populations
Population:	• HIV-infected persons age ≥ 18 years, English or Spanish speaking • Virally suppressed at time of enrollment (Cohort 1 or Cohort 2 - CAB-RPV LA cohorts)
Intervention:	CAB-RPV LA in CBOs
Objectives:	Pilot-test strategies for implementing CAB-RPV LA in non-HIV clinic settings
Design/Methodology:	Design: Three-arm cohort study comparing CAB-RPV LA delivered outside of standard clinical settings to CAB-RPV LA delivered in the HIV clinic setting and to standard care (HIV treatment delivered in the HIV clinic) utilizing EHR data Methodology: mixed methods (qualitative, quantitative)
Total Study Duration:	24 months for total study (Objectives 1-3) 12 months for Objective 2 only (current protocol); It is anticipated that final data analysis could take up to an additional 12 months.
Subject Participation Duration:	Six months.

1.0 Background & Rationale

1.1 Background

Studies have shown that People Living with HIV (PLWH) who stay in care, adhere consistently to ART, and achieve viral suppression have little to no risk of HIV transmission (Cohen et al., 2016); this means that ensuring retention and treatment adherence among PLWH is critical for HIV prevention. However, social determinants of health, such as poverty, homelessness, substance use, mental health disorders, and a history of incarceration, can elevate the risk of non-adherence and retention in traditional, clinic-based HIV care for some populations. The added complication of the COVID-19 pandemic and the resulting challenges around accessing medical care within traditional settings have made adherence increasingly difficult for PLWH. Alternative models to support ART adherence and retention in care are the foundation of achieving viral suppression and curbing HIV transmission for these vulnerable and high-risk populations.

Cabotegravir-Rilpivrine Long Acting (CAB-RPV LA) has been proven clinically effective and is fully approved by the FDA. In addition to its efficacy, CAB-RPV LA has shown promising potential as an alternative treatment modality to improve adherence for populations at the highest risk for falling out of care. CAB-RPV LA can be administered as a monthly or bi-monthly injection and thus may address multiple adherence-related challenges faced by high-risk populations, including the need to remember a daily pill, the lack of a place to refrigerate medications, and side effects, as the medication has been found to be well-tolerated (Swindells et al., 2019). Qualitative data collected in the first objective of this project have shown that a majority of patients interviewed would prefer the injection in comparison to their usual daily oral medication, and believe that an injection would increase their ability to adhere to treatment. They would also strongly prefer that injection to be delivered in a setting that they frequent, often outside of the HIV clinic.

At the same time, CAB-RPV LA requires a monthly or bi-monthly injection in order to be effective, thereby necessitating more frequent interaction with a provider than with oral HIV medication. Injection administration typically takes place in an HIV clinic or similar healthcare setting. This higher level of touch may present challenges for patients, including transportation costs, lost wages for visits during clinics' typical hours that coincide with the workday, and stigma. Patients also need to be engaged with their healthcare provider. Overcoming these barriers by facilitating and promoting CAB-RPV LA's acceptance and implementation in community-based settings and among patients, providers, and organizations will significantly contribute to ending the HIV epidemic.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and Boston Medical Center/Boston University (BMC/BU) Medical Campus Human Research Protection policies and procedures.

1.2 Rationale & Purpose

Our proposed implementation research is designed to evaluate a novel approach to engage individuals with HIV who are at the highest risk for not accessing care or adhering to treatment. We are not testing CAB-RPV LA; this is an approved drug. We are also not studying the drug nor are we studying it for a new population, new dosage or new route of administration. Rather, we are conducting an implementation study and propose to test implementation CAB-RPV LA in community-based settings.

Strategies to implement evidence-based interventions to end the HIV epidemic are urgently needed. Despite highly effective antiretroviral treatment (ART) for HIV infection and multiple effective prevention interventions, there are approximately 40,000 new HIV infections annually in the US (CDC, 2019). Two of the four pillars of the US Department of Health and Human Services "Ending the HIV Epidemic" initiative are to:

1) treat individuals with HIV rapidly and effectively to achieve viral suppression; and 2) prevent new infections by using evidence-based interventions (https://www.cdc.gov/endHIV/).

Our implementation research addresses three ViiV Healthcare priority areas: 1) implementation of CAB-RPV LA delivery models in non-HIV clinic settings; 2) feasibility and acceptability of bringing CAB-RPV LA injections to the patient (rather than bringing the patient to the medication in more traditional ways only); and 3) addressing challenges of CAB-RPV LA delivery amongst high risk populations, specifically women and men of color, immigrants, homeless individuals, active substance users, transactional sex workers, individuals released from incarceration, and individuals who have fallen out of HIV care. Our study (which overall incorporates three Objectives) addresses the following research questions:

A. Implementation Questions

1. Will community-based delivery of CAB-RPV LA be an acceptable and feasible delivery method to high-risk PLWH from the patient, provider and community organization perspectives? (acceptability/feasibility)
2. Can a community-based delivery strategy lead to initiation and completion of injections for six months for at least 80% of individuals who are enrolled into Cohort 1 for an initial visit in an outreach setting? (reach)
   See Section 11 for information on the details of the sample size calculations and Section 7.2 for how study staff will stay in contact with participants to maximize potential for longer term engagement.
3. What are the characteristics of patients who are most likely to have an initial injection and do these characteristics differ for individuals who receive CAB-RPV LA in and outside of the HIV clinic? (equity)
4. Are patients who are seen for CAB-RPV LA in community-based settings satisfied with their HIV care? (patient-centeredness)
5. Will consistent delivery of CAB-RPV LA be possible in community-based (non-HIV clinic) settings? (feasibility)
6. Will the providers at a drop-in center or community-based organization be willing to implement CAB-RPV LA within their non-traditional setting? (adoption)

B. Clinical Questions

1. Can individuals targeted for intervention at community-based delivery site achieve viral suppression and receive initial injection?
2. Can a community-based delivery strategy ensure engagement in services and receipt of CAB-RPV LA visits among high-risk populations? (effectiveness)
3. Is a community-based delivery strategy using CAB-RPV LA superior to the current standard of care in ensuring treatment adherence for individuals at highest risk? (effectiveness) Can high-risk individuals who receive community-based CAB-RPV LA be adherent to care, defined as undetectable viral load, for six months?

2.0 Objectives

The overall objective of this study is to use mixed methods to assess the feasibility and acceptability of delivery of HIV injectable medications outside of the traditional HIV clinic setting and within community-based settings serving individuals at high risk of not engaging in care. Specifically, we propose to examine a set of implementation questions and effectiveness/clinical questions as identified in Section 1.2 above.

3.0 Study Design

The study design for the overall study is a hybrid implementation-effectiveness study. We will used both qualitative and quantitative methods to conduct our work. Objective 2, the focus of the current protocol, will be a three-arm cohort study that uses quantitative methods. Our learning from this objective will be supplemented with qualitative data in Objective 3. In this study, we test our primary implementation strategy, changing the service delivery site to a community-based clinical intervention, while observing and gathering information on relevant clinical outcomes and community organization and clinical provider experiences.

Our overall analytic approach will include collecting qualitative data from potential patients, health care providers and community organizations related to feasibility and satisfaction with the model in Objectives 1 and 3; and quantitative Electronic Health Record (EHR) and participant survey data to address Objective 2 outcomes. Objective 1 has already been completed and included formative, pre-implementation work, specifically qualitative interviews, to assess intervention acceptability, feasibility, and appropriateness from the patient perspective that will help us define the final implementation blueprint for implementing the Objective 2 intervention. Objective 2 will be a cohort study comparing three groups: individuals who receive CAB-RPV LA at Project Trust, individuals who receive CAB-RPV LA in the HIV clinic, and individuals who share characteristics of Cohort 1 and are engaged in standard of care. Objective 3 will use qualitative methods to examine the in-depth experiences of patients who received CAB-RPV at the community site about their experiences and satisfaction with the model; and with health care providers and other individuals working in the community organizations regarding their experiences with the new service delivery model and plans for sustainability related to CAB-RPV LA treatment within their setting. Objective 1 was already approved by the BUMC IRB (protocol # H-40900; a protocol was not required by ViiV Healthcare for Objective 1 or Objective 3) and has been completed; **this protocol focuses on Objective 2 only.**

4.0 Potential Risks & Benefits

4.1 Potential Risks

The primary risk related to participation in the study is dropping out of care and not being linked to care. However, it is important to note that this is an ongoing risk for these patients in general given their social determinants of health putting them at higher risk of not being engaged in their care. There are risks related to the medication itself, which include injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, rash, diarrhea, pain/discomfort, nodules, induration, swelling, erythema, pruritus, bruising/discoloration, warmth and hematoma. Less common risks include gastrointestinal disorders, hepatobiliary disorders, weight increase, psychiatric disorders including anxiety (irritability, depression, abnormal dreams) and skin hypersensitivity. There is also the risk that if a participant is non-adherent to the injections, they may become resistant to cabotegravir and rilpivirine.

Special attention will be given to any medical issues related to the injections, including perceived soreness, fatigue, and other unintended consequences throughout the trial and standard referral to BMC will be made in such cases. It is important to note that CAB-RPV LA has been fully approved for use; the question for this study is NOT the effectiveness of the medication, but rather whether it can be delivered in non-traditional settings. Consent procedures will include detailed discussion of what the use of CAB-RPV LA will entail, both advantages and disadvantages, and an opportunity for the potential participant to ask questions. Once consent for screening has been provided,

study staff will confirm eligibility via EHR and conduct necessary testing (viral load, genotype). Study staff will contact potential participants within two weeks (once test results are received) and tell them if they are eligible for enrollment. If they are eligible, study staff will ask them to return for final study enrollment. All clinical data to determine eligibility will be collected from the EHR. There are also potential risks with the oral lead-in medications. Side effects of Vocabria include Headache, Nausea, Abnormal dreams, Anxiety, Insomnia. Side effects of Rilpivirine include Depressive disorders, Abnormal dreams, Rash, Abdominal Pain, Drowsiness, Dizziness, Vomiting, Nausea, Headache, Difficulty falling asleep or staying asleep. If participants choose to take the oral lead-in, they will be monitored throughout the oral lead in period for these side effects.

As with any study, there is the risk of loss of confidentiality as study personnel will have to access EHR data for individuals enrolled. However, we will ensure to take all precautions normally taken with use of EHR data in our institution, including only obtaining the data necessary to conduct the study. While study staff will need access to EHR data for purposes of ensuring eligibility, outcomes data will be obtained from the BMC Clinical Data Warehouse, which will be provided to the study team under strict protocols and will include study identifiers rather than names.

4.2 Potential Benefits

With new treatment advances, HIV is now a chronic disease that can be managed as long as PLWH remain adherent to ART. Yet, adherence is challenging for many individuals. Increased adherence to ART is a potential benefit for individuals, as are improved health outcomes as a result of greater adherence. It is hoped that providing treatment in alternative settings and via monthly injection rather than requiring adherence to daily pills will enable better adherence. This study can benefit other patients desiring alternative models and other institutions attempting to better keep higher risk persons adherent to care.

5.0 Study Subject Selection

5.1 Subject Inclusion Criteria

Cohort 1: Age ≥ 18 years, English or Spanish speaking, HIV-positive, labs indicate that they are a candidate for the medication and virally suppressed, meaning that their HIV-1 ribonucleic acid is less than 50 copies per mL. Individuals enrolled in Cohort 1 must be willing to complete the locator form (Appendix G) in order to receive appointment reminders prior to their monthly/bi-monthly injection and ongoing follow-up by outreach and study staff to maximize potential for adherence.

Cohort 2: Currently enrolled in care at CID and receiving CAB-RPV LA injection, age ≥ 18 years, English or Spanish speaking. Individuals enrolled must be willing to complete the locator form in order to receive appointment reminders prior to follow-up data collection.

Cohort 3: Enrolled in care at CID but not receiving CAB-RPV LA, age ≥ 18 years, matched to participants demographically and in terms of other characteristics in Cohort 1 at a 1:1 ratio. Individuals in Cohort 3 will be receiving the Standard Care for HIV treatment in CID. Standard of care for this group includes access to regular appointments with their HIV provider, oral ART, case management services, etc. Individuals enrolled must be willing to complete the locator form in order to receive appointment reminders prior to follow-up data collection.

Our goal for all three cohorts is to enroll a percentage of women that is equivalent to the number of female patients served by the sites, approximately 20-30% female. Similarly, we will ensure that our sample includes individuals of color proportional to their representation within the setting across all three cohorts.

5.2 Subject Exclusion Criteria

Individuals who are not HIV positive, individuals under the age of 18 and individuals who do not speak English or Spanish will be excluded. Individuals who are not virally suppressed prior to beginning CAB will be excluded (excluding Cohort 3). Individuals who are not willing to take CAB-RPV LA after detailed discussion of what the use of CAB-RPV LA will entail, or are unable to undergo clinical eligibility testing to confirm eligibility will be excluded (excluding Cohort 3). If they have a history of integrase inhibitor mutations suggesting resistance to Cabotegravir or Cabenuva, a history or evidence of resistance to either INSTI or NNRTI, are currently pregnant or breastfeeding, or have HIV 1 with an HIV 2 co-infection or an HIV 2 infection, they will also be excluded. Individuals who have hepatic impairment at baseline lab draws will be excluded. Individuals who are on drugs that have known interactions with Cabenuva (including but not limited to carbamazepine, oxcarbazepine, phenobarbital, phenytoin, St Johns Wort, systemic Dexamethasone, rifabutin, rifampin and rifapentine) will be excluded. Individuals who have chronic Hepatitis B infection will also be excluded.
If an individual is receiving CAB-RPV LA at CID, they are not eligible for Cohort 3.

6.0 Study Intervention

The study intervention for Cohort 1 is delivery of HIV medication at Project Trust, rather than in the BMC HIV Clinic. Project Trust (PT) is a street-based drop-in clinic that is focused on STD testing, treatment, harm reduction, and social services engagement. PT engages in outreach work, provides individuals with substance use disorder safe injection kits, and is a well-established community site for the target population frequenting the area, which is home to a high number of individuals who are homeless, diagnosed with substance use disorder, and are living with HIV. Study staff who will be administering the injection are all trained clinicians (either nurse practitioners or physicians) and are BMC staff. Individuals administering the injection will all be listed on the BUMC Internal Review Board study protocol.

There is not a clinical intervention or any intervention beyond data collection for Cohorts 2 or Cohort 3. Cohort 2 will be receiving their CAB-RPV LA within the BMC HIV clinic as their standard care. Cohort 3 will be receiving standard of care (not CAB-RPV LA) and will be patients of the BMC HIV clinic. Individuals enrolled in all three cohorts will be asked to complete a survey at study enrollment (baseline), between 2-4 months after their enrollment (midpoint) and a final follow up between 6 - 8 months post baseline. Clinical data will be obtained from the BMC EHR via the clinical data warehouse at these time periods and no other data will be collected directly from study participants for Objective 2.

7.0 Study Procedures

Medication regimen

	Cohort 1	Cohort 2
Month 1	*Optional Oral lead-in (up to 28 days)* 30 mg tablet of Vocabria 25 mg tablet of Edurant *Opt out of Oral Lead-In:*	(Anticipated) Maintenance Dose

	Initiation Injection (600 mg of cabotegravir and 900 mg of Rilpivirine)	
Month 2	*Oral Lead-in Completed*: Initiation dose (600 mg of cabotegravir and 900 mg of rilpivirine) *Oral Lead-in not done*: Maintenance Dose (400 mg of cabotegravir and 600 mg of rilpivirine)	*Monthly: Maintenance Dose* *Bi-monthly:* No Injection
Month 3	*Oral Lead In completed:* Maintenance Dose (400 mg of cabotegravir and 600 mg of rilpivirine) *Oral Lead In Not Done:* *Monthly:* Maintenance Dose *Bi-Monthly:* No Injection	*Monthly:* Maintenance Dose *Bi-Monthly:* Maintenance Dose
Month 4	*Oral Lead In:* *Monthly:* Maintenance Dose *Bi-Monthly:* No Injection *No Oral Lead In:* *Monthly:* Maintenance Dose *Bi-Monthly:* Injection	*Monthly:* Maintenance Dose *Bi-monthly:* No Injection
Month 5	*Oral Lead In:* *Monthly:* Maintenance Dose *Bi-Monthly:* Maintenance Dose *No Oral Lead In:* *Monthly:* Maintenance Dose *Bi-Monthly:* No Injection	*Monthly:* Maintenance Dose *Bi-Monthly:* Injection
Month 6	*Oral Lead-In:* *Monthly:* Maintenance Dose *Bi-Monthly:* No Injection *No Oral-Lead In:* *Monthly:* Maintenance Dose *Bi-Monthly:* Injection	*Monthly:* Maintenance Dose *Bi-monthly:* No Injection
Month 7	*Oral Lead In:* *Monthly:* Maintenance Dose *Bi-Monthly:* Injection *No Oral Lead In:*	*Monthly:* Maintenance Dose *Bi-Monthly:* Injection

	Monthly: Maintenance Dose *Bi-Monthly:* No Injection	

7.1 Cohort 1 Recruitment, Screening & Enrollment
Cohort 1 Recruitment and Screening:

Project Trust Recruitment: When an individual who appears to meet the inclusion criteria for Cohort 1 presents at PT, the ARCH outreach worker or PT staff will inquire about their interest in participating in the study. For those who are interested, PT staff will make a warm handoff to study staff.
Faster Paths Recruitment: Faster Paths is a substance use urgent care clinic at BMC that helps patients access substance use treatment as well as HIV testing and care. When an individual who meets study criteria presents to Faster Paths, the Faster Paths clinicians will inquire about potential interest in study participation. If the individual indicates they are interest, the Faster Paths staff will make a warm handoff to study staff.
Boston Living Center: The Boston Living Center is a program located in the Back Bay that serves people living with HIV. In order to utilize Boston Living Center programs, individuals must present both a diagnosis letter as well as a referral letter. Study staff will set up a table during their lunch service, which all Boston Living Center members are eligible to participate in, and have a study flyer that details the study information and inclusion criteria. If individuals indicate that they are interested in participation, study staff will have conduct the screening consent with them utilizing the Screening Consent Form (Appendix A) as well as have the potential participant sign a Release of Information if they indicate they are not a current BMC patient.

It will be necessary to confirm that all potential participants are eligible for the study. To make this determination, study staff will consent the potential participant to access their Electronic Health Records using the Screening Consent Form (Appendix A).

- If a potential participant indicates that they are not a current BMC patient and receives their care elsewhere, study staff will request that the potential participant sign a Release of Information so that a study clinician may contact their current provider to obtain documentation of their care history in order to complete the eligibility screening, as well as discuss with their current provider whether the potential participant is a good candidate for the monthly or bi-monthly injection.
- If a potential participant is a BMC patient, study staff will obtain consent to move forward with the participant's care team in order to determine that the potential participant is eligible for the study.

All decisions will be made by study clinicians who will review medical documentation to determine that the potential participant meets eligibility criteria. Participants must be virally suppressed prior to enrollment, meaning that their HIV-1 ribonucleic acid measures less than 50 copies per mL. If a potential participant's EHR review indicates that they have a history of integrase inhibitor RT mutations suggesting resistance to Cabotegravir or Cabenuva, have demonstrated they have resistance to either an INSTI or an NNRTI, that the potential participant is currently pregnant, breastfeeding, or that the potential participant has HIV 1 with an HIV 2 co-infection or an HIV 2 infection, they will be deemed to be ineligible. Individuals who are not HIV positive, individuals under the age of 18 and individuals who do not speak English or Spanish are also ineligible. Individuals who are not virally suppressed are ineligible. Individuals who are not willing

to take CAB-RPV LA after detailed discussion of what the use of CAB-RPV LA will entail, or are unable to undergo clinical testing to confirm eligibility will be excluded. Individuals who are on drugs that have known interactions with Cabenuva, including but not limited to carbamazepine, oxcarbazepine, phenobarbital, phenytoin, St Johns Wort, systemic Dexamethasone, rifabutin, rifampin and rifapentine. Individuals who have chronic Hepatitis B infection will also be excluded. All women with child-bearing potential will have a pregnancy test conducted at a CLIA approved lab to rule out pregnancy.

Study staff will contact every individual who was screened within two weeks of screening (once test results are received and study clinician has confirmed whether or not they are eligible) and let them know if they are eligible for enrollment. Study staff will ask eligible individuals to return to PT for final study enrollment. If the potential participant is ineligible for enrollment due to being unsuppressed, study staff will encourage the potential participant to re-engage in their care in order to achieve suppression, and reach out to study staff once their viral load is undetectable for enrollment. If potential participants are ineligible for enrollment based on other criteria, study staff will refer back to clinical staff from PT to make an appropriate referral.

Once an individual in Cohort 1 is determined eligible and agrees to participate, they will meet with study staff at PT to complete the consent form to enroll in the study. Study enrollment will involve the following procedures:

- Study staff will contact the participant within 2 weeks of initial screening if participant is eligible for participation to schedule a meeting date for full consent procedures, and to collect baseline questionnaire data, as described above. Study staff will log this contact in the study log book (Appendix H).
- Prior to the consent and initial survey meeting, study staff will create a folder that contains a copy of the participant's screening consent form (Appendix A), a blank enrollment consent form (Appendix B), a blank Electronic Health Record Review Form (Appendix E), a blank Participant Questionnaire (Appendix F), and a blank Locator form (Appendix G). This folder will be labeled with their individual Study ID. The study ID key will be the following: Study ID Key: O2XXX – XXX is the equivalent of the number patient that they are. For example, the first person to be consented and enrolled into the study will be Participant Number O2001. The project manager will assign this number when participants are enrolled. This key will be used for participants in all three cohorts.
- Participants will have the consent form read to them and be asked to sign the consent form. These consent forms will be stored separately from data collection forms and will be kept in a locked filing cabinet. Study staff will be the only individuals who have access to this cabinet. The participant will have opportunities throughout the consent process to ask questions to both study staff and study clinician. After all questions are addressed to the participant's satisfaction, the baseline questionnaire will be completed.

Cohort 1 study intervention

All activities will be done on label. Therefore, before beginning CAB-RPV LA, participants who are meet the clinical criteria will discuss transitioning to the CAB+RPV oral RPV lead in if the participant and clinician choose to. The CAB-RPV LA oral lead-in is optional, which is FDA approved and on label. If the participant and their provider choose to begin the CAB+RPV oral lead-in, the procedure will take place as follows:

- Participants may be initiated onto a maximum 4 week CAB+RPV oral lead-in to monitor for side effects. The oral lead-in is comprised of one 30 mg tablet of Vocabria, and one 25 mg tablet of Edurant. Initial lab draws will include Genotype, HIV Viral Load, T Cell Subset, Comprehensive Metabolic Profile (which includes LFTs). Labs can be drawn at either the Shapiro Phlebotomy Lab,

or directly at Project Trust. If labs are drawn at Project Trust, PT staff will bring all lab tubes to Shapiro lab following standard Project Trust procedure. If participants choose to take the oral lead-in, they will be asked to complete the full 28 day course. If participants choose to take the oral lead-in, they will also be asked to check in with Project Trust staff weekly to monitor for adherence and assess any potential adverse events.

- Study staff will confirm with participant the date of their first injection. This contact will be recorded in the study Log Book (Appendix H). Study staff will confirm with clinician at PT the time and date of injection.

If the participant chose's to not take the oral lead-in mediation, the participant will proceed directly to the initiation injection once they have completed all required lab work, including HIV labs confirming that they are virally suppressed (> 50 copies per mL), and a comprehensive metabolic panel. The participant and their clinician will determine a date for the initiation injection. As the medication will need to be obtained from the pharmacy, participants will not be able to receive their initiation injection on the same day as they are enrolled into the study.

- At the time of the injection, during the 15 minute waiting period, study staff will sit with the participant and remind them of the target date for the next injection. This date will be recorded in the study Log Book. The month following the initiation dose, participants receive a maintenance dose. Once the participant has received the maintenance dose, the participant and their clinician may discuss whether the participant would like to shift to receiving the injection every other month rather than every month. The clinician and the participant may choose whether to receive the injection every month, or every other month per CID standard of care and the medication package insert.
- One week prior to each scheduled injection date, study staff will contact participant via their preferred contact method determined on the Locator Form to confirm injection date and confirm with the community-based clinician administering the injection.
- One day prior to injection date, study staff will contact participant for reminder.

Below is a table that outlines when all evaluation activities occur:

Month	Cohort 1	Cohort 2	Cohort 3
1	• Screening • Enrollment • Comprehensive Metabolic Panel • Baseline Data Collection • Participant may choose to take 28 days of Oral Lead-In medication • If participant opts out of the oral lead-in, they will receive their Initiation Injection during this time point	• Screening • Enrollment • Baseline Data Collection	• Screening • Enrollment • Baseline Data Collection
2	• Oral lead-in: Initial Injection • No Oral Lead-In: Maintenance Dose		

3	• Potential Midpoint Data Collection • Oral Lead-in: Maintenance Dose • No Oral Lead-in: *Monthly:* Injection, *Bi-Monthly:* No Injection	• Potential Midpoint Data collection	• Potential midpoint data collection
4	• Potential Midpoint Data Collection • Oral Lead-In: *Bi-Monthly:* No Injection, *Monthly:* Injection • No Oral Lead-In: *Monthly:* Maintenance Dose, *Bi-Monthly:* Injection • Comprehensive Metabolic Panel	• Potential Midpoint Data Collection	• Potential midpoint data collection
5	• Potential Midpoint Data Collection • Oral-Lead In: *Monthly:* Maintenance Dose, *bi-Monthly:* Injection • No Oral Lead-In: *Bi-Monthly:* No Injection, *Monthly:* Injection	• Potential Midpoint Data Collection	• Potential midpoint data collection
6	• Oral Lead-In: *Bi-Monthly:* No Injection, *Monthly:* Injection • No Oral Lead-In: *Bi-Monthly:* Maintenance Dose, *Monthly:* Injection		
7	• Oral Lead-In: *Bi-Monthly:* Maintenance Dose, *Monthly:* Injection • No Oral Lead-In: *Bi-Monthly:* No Injection, *Monthly:* Injection • Potential endpoint Data Collection	• Potential Endpoint Data collection	• Potential endpoint data collection
8	• Potential endpoint Data Collection	• Potential Endpoint Data Collection	• Potential Endpoint data collection
9	• Potential Endpoint data collection	• Potential endpoint data collection	• Potential endpoint data collection

7.2 Cohorts 2 & 3 Recruitment, Screening & Enrollment

Cohort 2 Recruitment and Enrollment: Participants for Cohort 2 will be individuals who are receiving HIV in care at BMC's Center for Infectious Diseases (CID) and are receiving CAB-RPV LA. CID pharmacists and providers will approach all individuals who are actively receiving CAB-RPV LA and assess whether they are interested in participating and ask them to complete the Screening Consent (Appendix C). If individuals are interested in participation, they will be given a warm handoff to study staff. Study staff will meet with patients at CID to complete the enrollment consent form (Appendix D). Participants will also be asked to complete the participant questionnaire at the baseline, midpoint (2-4 months post baseline) and endpoint (at least 6 months post baseline). They will also be asked to complete the Locator Form (Appendix F). Participants will enter the cohort and contribute data to the study from their first CAB-RPV LA injection and be followed in the EHR for a period at least 6 months to determine engagement in care and adherence. Data on clinical endpoints (appointment adherence, viral load, CD4, drug use etc.) will be collected from the EHR.

Cohort 3 Recruitment and Enrollment: EHR data will be used to match patients for Cohort 3 1:1 to patients in Cohort 1 based on the following variables: history of drug use, housing status, sex. Patients in cohort 3 will be a prospective cohort of patients who are HIV positive and not receiving CAB-RPV LA. The Clinical Data Warehouse will match 10 participants to every 1 enrolled in Cohort 1 based on the variables above. CID staff will approach potential participants to assess interest in participation. If individuals are interested in participating, they will be given a warm handoff to the project manager to complete the Enrollment Consent form (Appendix D). They will also be asked to complete the Locator Form (Appendix G).The remainder of their study activity will mirror that of Cohort 2.

7.3 Data Collection

Objective 2 will include two forms of data collection: 1) participant questionnaires at enrollment (baseline), midpoint (2-4 months), and endpoint (at least 6 months post enrollment) follow-up; 2) clinical and appointment data from the EHR. The baseline questionnaire will be administered to all participants at the time of consenting to participate in the study in order to collect basic sociodemographic characteristics, such as gender identity, education, marital status, income, residence, and other characteristics shown to influence ART outcomes (Mills et al., 2006). The questionnaire will also collect data on potential predictors of intervention success, including unmet needs, satisfaction with care and stigma. (Appendix F). At the midpoint (2-4 months post enrollment) and endpoint (at least 6 months post enrollment), the data will be collected again, using the same data collection instrument. The midpoint data collection and endpoint data collection target dates will be determined by study staff and participants at the first enrollment appointment. For Cohort 1 and Cohort 2 participants, these dates will coincide with their scheduled injections if possible, for convenience.

One week before each target data collection date, study staff will contact the participant using the preferred communication method they specified on their Locator Form at enrollment. Once a data collection date has been determined, study staff will contact participant through their preferred means of communication one day prior to appointment for a reminder.

At the time of data collection, the participant and study staff will meet at determined study location (either Project Trust or CID). Study staff will bring the Participant Folder, Log Book and a ClinCard. The participant will complete the participant survey. If the participant is in Cohort 1 or 2 and is scheduled to receive their

injection at this appointment, the survey can be completed during the 15-minute observation period after the injection.
The clinical and appointment data to be collected from the EHR on all study participants will include clinical endpoints (appointment adherence, viral load, CD4, etc.). Data on clinical endpoints will be collected from their EHR at enrollment at each data collection period using the Chart Review Tool (Appendix E).

All study participants will be provided a ClinCard worth $25 once they have completed the baseline survey. ClinCards will be kept in the same locked filing cabinet as participant folders and the Log Book. Study staff are all trained in how to register and activate the ClinCard. ClinCards will continue to be provided at the completion of the three-month and six-month follow-up surveys. Each time a participant receives a ClinCard, it will be recorded in the Log Book. Completed Surveys will be kept in the Participant Folder, to be placed in the locked filing cabinet of the Project Manager.

7.4 Clinician Training

All clinicians who are to administer CAP-RPV LA in any setting related to this study will complete full Good Clinical Practice training, and have read the Cabenuva instructions for use, all information regarding contraindications, warnings and precautions, drug interactions, and possible adverse effects. The package insert will be attached to the BUMC IRB submission. All clinicians administering injections will review the ViiV Healthcare Cabenuva training video and participate in injection training.

All clinicians will be trained by ViiV in administering intramuscular gluteal injections. All study staff will be trained in the cold chain storage procedure, including transportation requirements and thawing instructions by BMC Pharmacy Staff. All clinical study staff have basic life support training and are CPR certified. All clinical study staff will be trained during a staff meeting on adverse event reporting per both BMC and ViiV. Adverse Event Reporting forms will be those specified by ViiV and will be attached to the IRB submission.

All clinical staff are familiar with non-traditional care setting sites, and when off site will follow the protocols set forth by staff at those sites. All study staff are aware of and trained in how to follow adverse event protocol (see Sections on Adverse Events, Serious Adverse Events and Post Injection Reactions" for specific protocol details). This training will occur at a clinical study staff meeting at Project Trust, which is located adjacent to the BMC campus. In the case of serious adverse events, participants will be brought to the BMC Emergency Department.

7.5 Medication Acquisition and Storage

For the optional oral lead-in, the study clinician will write the prescription for the participant and send it to the BMC pharmacy. Depending on the participants preference, either PT staff or the participant themselves will go pick the prescription up from the pharmacy and the participant will begin taking the oral lead-in medication on that day. The participant will keep their medication for the duration of their lead in.

In order to keep CAB-RPV LA at the determined temperature necessary, (2°C to 8°C; 36°F to 46°F), the medication will be kept in a cooler bag from the time that it is picked up from the BMC pharmacy until it is brought over to PT to be stored until use. The refrigerator at PT is in the Nurse Practitioner's office; the refrigerator itself has a locked door, and the office door is also locked when not in use. The refrigerator is temperature monitored in conjunction with BMC requirements. A study clinician will write the CAB-RPV LA prescription and submit through Epic, the EHR system employed by BMC. The study clinician will go through the prior authorization procedure in collaboration with the specialty pharmacy. The specialty pharmacy team and study staff will have a standing weekly check-in to determine how many injections are scheduled for

each week. The study staff will then go pick up all the prescriptions for the week at the pharmacy, and transport them to PT in the cooler bag. Staff will wait until participant has arrived at Project Trust to remove the injection from the refrigerator to begin the thawing process. If the participant does not show up for their scheduled injection, the medication will be left in the refrigerator until the participant is ready for administration.

7.6 Injection Process and Safety Procedures

For patients enrolled in Cohort 1, injection procedures will be as follows:

- 15 minutes prior to the scheduled appointment time, the study clinician will remove the injection from refrigeration.
- Injections will be administered by a licensed healthcare professional (physician, nurse, nurse practitioner).
    a. A complete dose will include two injections: one injection of cabotegravir and one injection of rilpivirine.
    b. Each injection will be administered at separate gluteal injection sites during the same visit, with the ventrogluteal site recommended.
    c. The clinician will consider the body mass index (BMI) of the patient to ensure that the needle length is sufficient to reach the gluteus muscle. Longer needle lengths (not included in the dosing kit) may be required for patients with higher BMI (greater than 30 kg/m2) to ensure that injections are administered intramuscularly as opposed to subcutaneously.
- The clinician and the participant will determine the target date for the next injection, which will occur between 25-32 days from initial injection. This discussion will happen while the participant waits for 15 minutes to ensure that no immediate adverse effects occur. This encounter and next planned injection date will be documented in the study Log Book by study staff. During this 15-minute period, the participant may also complete follow-up questionnaires if they are due for their three-month or six-month follow-up survey.
- Once the participant receives their second injection, they may discuss with their clinician whether they want to continue to receive their injection monthly, or whether they want to move to a bi-monthly schedule. The same procedures (confirming appointments in advance, removal from refrigerator, injection administration, monitoring period post-injection, scheduling of next injection, documentation in study log) will be used for follow-up injections
- Once the participant has been enrolled for at least 6 months in the study, they will be given the option to remain on CAB-RPV LA
    a. That administration can take place either at PT or at CID depending on the participants preferences
    b. If the participant wishes to receive their injection at CID, the study clinician will reach out to the participants CID provider so that the participant can begin to schedule their injections at CID

7.7 Missed Injection Target Dose Timeline

In order to ensure that patients receive their injection within the 7 days of their target injection date, the following outline will be followed. This outline is applicable for any missed dose:

- **Day 1 Post Target**: The study team will outreach to the participant via their preferred communication method as specified in their locator form in order to encourage them to return within the following three days. The encounter will be tracked in the study Log Book.
- **Day 3 Post Target:** The study team will outreach again to the participant via the preferred communication method to encourage them to return the following day. The encounter will be tracked in the study Log Book.
- **Days 5-7 Post Target:** The study team will enlist BMC's ARCH and PT street-based outreach workers who are experienced with and successful at reaching and engaging high-risk patients. The outreach workers will conduct active outreach to the participant in the community to bring them in for a visit. If active outreach is unsuccessful, the study team will also use the contacts on the locator form to attempt to reach the participant. The encounter will be tracked in the study Log Book.
- **Upon Return Within 14 Days Post Target:** The study clinician will obtain a viral load and genotype. If the participant's viral load is less than 200 copies per mL, they will administer the CAB-RPV LA. If the participant's viral load is over 200 copies per mL, the study clinician will refer them to their primary care provider who will make the determination about whether or not an injection is appropriate. The encounter will be tracked in the study Log Book.
- I**f participant returns after 15 days Post Target:**
    - **Missed Dose Occurs within 2 months of Initiation Injection:** The participant will be given a maintenance dose at their next contact with study staff (400mg/600mg 2 ml). The participant will then resume their normally scheduled injection plan, i.e. next injection scheduled to be given 25-32 days after maintenance dose administered.
    - **Missed Dose Occurs after first 2 months of injection:** The participant will be given a loading dose instead of their scheduled dosing amount (600mg/900 mg 3 ml). The participant will then resume their normally scheduled injection plan.

7.8 Dosing Errors & Other Errors

All efforts will be made to ensure there are no dosing errors. However, the following procedures are in place to address dosing errors or other errors:

- **Dosing Error – Too Large of a Dose Administered:** The study staff will contact the participant immediately following recognition of error and inform them about their error. If dose was the equivalent or higher of the loading dose (600 mg/900 mg 3 ml), then study staff would change next target injection date to be 2 months after dose given in error, and then resume maintenance doses moving forward.
- **Dosing Error – Too Small of a Dose Administered:** Study staff will contact the participant immediately following the recognition of the dosing error.
- **Incorrect storage of Cabenuva**: If it is determined that the injection has been incorrectly stored, the affected doses will be disposed of in a hazardous waste container.
- **Healthcare Provider Needlestick Injuries:**
    - Wash/rinse wound or exposed area immediately.
    - Report incident to Study Staff Supervisor

- Exposed individual should call the BMC Working Well Clinic at 617-638-8400 or visit the clinic on the 7th floor of the Doctor's Office Building.
- Print and Complete all forms listed below that are found on the BMC Employee Hub:
  - Blood and Bodily Fluids Exposure Incident Form and scan and email to working.wellClinic@bmc.org
  - Source Patient Requisition Form
  - Source Patient Testing Release Form – other staff member must consent patient, have both printed name and signature at the bottom of the page of source patient and ordering provider who consented patient
  - Test results are reported to the Working Well Clinic who will notify individual of results

7.9 Adverse Events, Serious Adverse Events and Post Injection Reactions

Adverse Event (AE) Definition: An AE is any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. 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. An adverse event (AE) does not include medical or surgical procedures, although the condition that led to the procedure may be an AE, or situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions). Any medical condition or clinically significant laboratory abnormality with an onset date before baseline are considered to be pre-existing conditions and should be documented as medical history.

Adverse Drug Reaction (ADR): An adverse drug reaction is defined as a noxious and unintended response to a medication related to any doses where there is at least a reasonable possibility of a causal association between the medication and the AE, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or ViiV as having a reasonable suspected causal relationship to the drug qualify as adverse reactions. Note: Injection site reactions are considered drug related as they are related to the administration of Cabenuva.

Serious Adverse Event (SAE): A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization unless hospitalization is for:
  - Routine treatment or monitoring of the studies indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study drug.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of SAE given above and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

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. A serious adverse reaction (SAR) is an adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the study product, based on the information provided. “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above. All SAEs whether related or not to Cabenuva will be collected in this study. Prompt notification to ViiV of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of Cabenuva are met.

Medical Device Deficiency/Incident Definition: A device deficiency/incident is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. These can include malfunctions, use errors, and/or deficiencies in information supplied by the manufacturer. Device deficiencies/incidents may result in an SAE (including death or serious deterioration in health of a participant or other non-participant person).

Assessment and Treatment of Adverse Events and Serious Adverse Events: Health care providers administering the injection and any qualified designees are responsible for detecting, documenting, and reporting events that meet the above definition of an AE or SAE from the time of the informed consent to study termination. Health care providers administering the injection should send all reported Adverse Events and Serious Adverse Events to the Principal Investigator and Study Clinician for follow up medical management and to determine relatedness to the injection. After the initial Adverse Event/Serious Adverse Event report, the study clinician or clinician administering the injection will proactively follow the participant at all subsequent injection visits and study contacts. All Serious Adverse Events will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Post-Injection Reaction: In the case of a post injection reaction, including, but not limited to, dyspnea, bronchospasms, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain, participants will be monitored for 15 minutes post injection. Oxygen, epinephrine, intravenous fluids, corticosteroids, antihistamines and subcutaneous adrenaline will all be available on site at Project Trust. Offsite, epinephrine, corticosteroids, antihistamines and subcutaneous adrenaline will be brought with clinical staff. If participant’s status indicates that they need oxygen, intravenous fluids, or their status is declining, emergency services will be called and the participant will be brought to the Boston Medical Center emergency department. While onsite at Project Trust, if a reaction lasts longer than 30 minutes, or the participant shows signs that their clinical condition is declining, emergency services will be called immediately.

7.10 Accidental IV Administration

In the event of a suspected accidental IV administration, clinical staff will monitor participant’s viral load within 2 weeks of IV administration.

7.11 Clinical Management of Participants

Many patients will already be Boston Medical Center patients, and will continue to see their usual Infectious Disease provider during the entirety of the study. Clinical decisions

around patients and the clinical management of missed doses, serious adverse events and adverse events will be managed by the Infectious Disease clinical providers who are on the study staff. Participants who are new to Boston Medical Center will have a new patient MRN assigned to them, and will be assigned to the clinical patient panel of one of the CID providers on the study staff. All clinical decisions about patients will be made by their healthcare providers. Whether to continue or discontinue Cabenuva if a participant becomes pregnant will be decided by the study clinicians in collaboration with the participant's CID provider that will also include a full review of the participant's case and medical record. All participants will continue to be offered all their regular services as before, including care in the CID, relapse prevention and harm reduction services, STI education and counseling, and all other needed services. Study staff will monitor for depression using the same procedures as CID.

8.0 Safety Reporting

8.1 Safety Reporting to ViiV

Healthcare providers administering the injection and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE from the time of the informed consent to study termination. As described in Section 7.9 above, healthcare providers administering the injection will send all reported AEs and SAEs to the Principal Investigator and the Study Clinician for follow up medical management and to determine relatedness to the injection. Treatment related to AE or SAEs will be recorded in the EHR and in the study logbook. ViiV will be informed of all these events. The Principal Investigator and the Study Clinician will be responsible for assessing AEs and SAEs for causality and for final review and confirmation of accuracy of event information and assessments.

All treatment-related Non-Serious AEs and Adverse Drug Reactions will be recorded in the "Non-Serious Adverse Event/Adverse Drug Reaction (AE/ADR) Pages" provided by ViiV. A blank, printed copy of this document will be kept in the locked filing cabinet along with the Log Book. Providers will be asked to fill out the document at the time that the Non-Serious AE occurs, and provide the document to the Principal Investigator who will fax the "Non-Serious Adverse Events/Adverse Drug Reaction (AE/ADR) Pages" document to ViiV within 5 days of the event occurring.

Assessment of Causality for Injection: The relationship of the injection to each AE will be assessed taking into consideration the following:

- A reasonable possibility is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The HIV clinician will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The USPI for marketed products will be used in consideration of this assessment.

The terms to assess the relationship of an event to study agent are:

Related: There is a reasonable possibility an event may be related to Cabenuva.
Not Related: There is not a reasonable possibility an event is related to Cabenuva

Adverse Events to Be Documented in this Study:

- All AEs and SAEs considered to be related to oral CAB or oral RPV.
- All SAEs in participants exposed to the injection, regardless of Principal Investigator or clinician assessment of causality.
- All AEs considered related to Cabenuva, with the exception of certain non-serious local Injection Site Reactions (listed below)

- All medical device incidents with Cabenuva
- All pregnancies in participants exposed to the injection

Injection Site Reaction: Injection Site Reactions (ISR) are considered drug related events, as they are related to the administration of Cabeuva. Localized non-serious ISRs with Cabenuva (redness, itching, swelling, pain or discomfort) are well characterized as described in the USPI, as such, these events will not be reported to ViiV as part of the study. However, any ISRs meeting serious criteria (complications of ISRs such as cellulitis, abscess) will be reported to ViiV, using the SAE reporting form.
Post Injection Reaction: All suspected post injection reactions whether serious or non-serious will be reported to ViiV.

8.3 Procedure for Reporting to ViiV

All SAEs associated with administration of the injection will be reported to ViiV global safety case management within one business day of the first awareness using the SAE Case Report Form. A copy of this form will be kept on site. Non-serious drug related AEs to the injection will be reported within 5 calendar days of first becoming aware of the vent, with the exception of certain non-serious localized ISRs (listed above) which are not subject to these reporting requirements. In addition, notification about all SAE's considered related to VOCABRIA or to EDURANT identified during the course of the study will be notified to ViiV within 1 business day of the Sponsor's awareness.

The Individual Case Safty Reports will be sent to ViiV as follows:

Email for Clinical Safety Mailbox: oax37649@gsk.com
Fax: +44 (0)20 81814780

Medical Device Incidents: Cabenuva is provided with vial adapters, needles and syringes for administration and is considered a combination product with a device component that is subject to regulatory post marketing safety reporting requirements. For I-TRAINS, the Principal Investigator will be responsible for the detection and documentation of events meeting the definition of device incidents/deficiencies that occur during this study. Should any person—either a study participant, or an associated person (non-study participant, e.g., a caregiver), or member of site staff—experience a device deficiency/incident, then a device deficiency form will be completed and sent to the sponsor within 24 hours of site awareness by the Principal Investigator. A copy of the form which includes instructions for reporting study participant and non-study participant information will be kept on site and is appended to this protocol (Appendix I).

Pregnancy: Participants of child-bearing potential will be reminded to inform their HIV provider immediately if they suspect that they are pregnant. If a pregnancy is reported, staff administering the injection will withhold the injection and the study clinician will record pregnancy information on the appropriate form and submit it to ViiV within 24 hours of learning of the pregnancy. The study clinician make the assessment, as described in Section 7.11, Clinical Management, above and discuss with the participant whether or not to continue the injection after making a benefit risk assessment. The pregnancy will be followed to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) will be considered SAEs and reported as such. Prior to continuation of the injection following pregnancy, the following will occur:

- The study clinician will confirm that the injection can be continued, will document this, and this documentation will be stored within the participant file documents.

- The study clinician will reach out to ViiV and the BUMC IRB to obtain written approval. Staff administering the injection and the treating HIV clinician will monitor the outcome of the pregnancy and the status of the participant and their offspring.

Pregnancy Reporting to ViiV: Any pregnancy that occurs during study participation will be reported to ViiV Healthcare by the Sponsor within one week of first learning of its occurrence. The pregnancy should be followed up to determine its outcome and reported to ViiV Healthcare. SAEs occurring in association with a pregnancy after the participant has completed the study and considered by the HIV treating physician as possibly related to CABENUVA, will be reported to ViiV Healthcare/GSK within 1 business day of awareness.

It will be the responsibility of ViiV Healthcare/GSK's central safety department to forward information on pregnancies to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://apregistry.com/index.htm.

Blank printed copies of all ViiV required documentation including the AE/ADR Intensity Form, Associated Person and Safety Reporting Information and Authorization Letter, IDSL Pregnancy and Pregnancy Notification Form, and Medical Combined Device Deficiency Form will be kept in folders at the study site. Copies of all required documentation will also be kept on the internal secure project drive.

9.0 Safety Review

This study is not intended to assess the efficacy of CAB-RPV LA as a medication; rather it is an implementation study to examine changing the service site of care delivery. CAB RPV-LA is already an approved medication that can be delivered to PLWH who receive care at CID. Thus, a DSMB is not required. However, in order to monitor safety of study participants in the pilot implementation trial, we will do the following: Any issues with the injections themselves will be recorded in logbooks. Special attention will be given to any medical issues related to the injections, including perceived soreness, fatigue, and other unintended consequences throughout the trial and standard referral to BMC will be made in such cases. We will also report all medication errors identified to the sponsor as required by ViiV. During analysis, we will categorize the errors into the four groups identified by ViiV in order to capture severity: medication errors associated with adverse events, medication errors without harm, intercepted (near miss) medication errors, and potential medication errors. VH has requested that all implementation studies involving the use of medications collect and report the following potential medical errors associated with administration of a medication: 1) Dosing errors, including incorrect loading dose, multiple loading doses, errors in maintenance dose (e.g. 3ml given instead of 2ml by accident), excess dose (e.g. two injections of one medication instead of one injection of each); 2) Faulty technique, including accidental IV or SC leading to partial IV administration, needle breakage, use of wrong needle, failure to fill syringe with medicine appropriately, multiple injections /re-injection on the same site (minimum gap), leakage from vial or syringe, leakage from injection site, healthcare provider needlestick injuries; 3) Other medication errors including delivery at a site other than the gluteal region, one injection of each drug but not on the same visit, storage at the wrong temperature, time outside refrigeration, use of expired medicine. These events will be reported through the Non-Serious Adverse Events/Adverse Drug Reaction Pages, Associated Person Safety Reporting Information and Authorization Letter, Medical Device or Combination Product with Device Deficiency/Incident Report Form, all attached in the Appendix of this document

We will also meet ViiV's expectations, including submission of all safety reports to all concerned parties, as well as reporting to concerned regulatory authorities. Medical governance for the study (i.e., welfare of the study population), in accordance with ICH Good Clinical Practice (GCP) all local regulations and legal requirements applicable to the study will be followed. Although this is an implementation study and safety incidentsare unlikely, we will also report to ViiV the following safety information within their pre-specified timeframes: 1) serious adverse events (SAEs) and pregnancy reports for subjects exposed to VH medications during the course of the study using the VH SAE and/or pregnancy case report form pages; 2) any other significant safety issues relating to the VH study medication. Medical events related to underlying HIV disease will also be collected, reviewed by the infectious disease study clinician on our study team, and followed throughout the trial. This clinician will also review or provide consultation for each SAE as needed. These reviews will include an assessment of the possible relatedness of the event to the study procedures. The study clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In the case of SAEs or AEs, the study clinician will complete the SAE/AE Drug Reaction pages and fax them to ViiV within 5 days for an adverse event, and within 24 hours/1 business day for serious adverse events per ViiV requirements. This document is attached to the IRB submission and is titled, "AE ADR Intensity GSK."

10.0 Data Handling and Record Keeping

10.1 Confidentiality

At the screening consent appointment, participants will complete the HIPAA Authorization to grant permission to study staff to review their EHR. After an individual provides informed consent for screening and HIPAA authorization, a clinician will review their most recent labs for genotype and viral load, which would typically be part of standard care, to determine if they are eligible for CAB-RPV LA. Results of this review will be used to determine final eligibility. Following this, the EHR will be reviewed at 3 months and 6 months to document information needed to evaluate outcomes using the Chart Review Form. Other clinical and demographic information will also be abstracted to enable investigators to better characterize the study sample and to use as covariates in analyses. There will be no additional clinical records kept specifically for the study. As CAB-RPV LA is one standard of care for HIV, record of injections received will also be recorded in the EHR. All study data will be stored on a secure, password protected computer. Additionally, although no personal or identifiable data will be collected beyond the informed consent form, all documents created, such as those related to analyses and findings, will be maintained in a locked filing cabinet and in a password-protected database only accessible to the researchers.

10.2 Study Records Retention

All data will be stored and maintained in line with current ethical standards. Personal and identifiable data will need to be collected for this study, including a locator form and other clinical data. Survey data on paper forms will be maintained in a locked filing cabinet and will not be linked to the informed consent document, which will be kept in a separate file. Each participant will be given a study identifier; the only document that will link individual names to this identifier will be a list maintained in a locked filing cabinet. A separate list will link the MRN to the identifier. Medical record numbers will not be included on any study data collection forms; only the study identifier will be used on data collection instruments. All documents created will be maintained in a locked filing cabinet and in a password-protected database only accessible to the researchers. All data will be maintained for seven years after the study is completed and then destroyed. The informed consent documents will also be destroyed at this time.

11.0 Statistical Plan

11.1 Study Hypotheses

Objective 2 has the following hypotheses:

- **H1:** Changing the service site will result in ≥ 80% of participants in the community-based intervention arm beginning injections
- **H2:** Of participants in the community-based intervention arm who begin injections, 80% will complete 6 injections
- **H3**: Changing the service site will result in improved engagement in care for participants in the community-based intervention arm compared to matched controls (Cohort 3) at 6 months for intervention patients compared to control group patients
- **H4:** Changing the service site will result in superior HIV viral suppression at 6 months compared to for participants in the community-based intervention arm compared to matched controls (Cohort 3)
- **H5:** Participants in the community-based intervention arm will be equally satisfied with their care compared to patients who receive care in clinic settings (Cohort 2).

11.2 Sample Size Calculation

For the pilot study, we have powered our study to address hypothesis 4 above. Our power calculation is as follows: With a total of 60 participants, 20 patients in each cohort, the study will have the statistical power to detect clinically meaningful differences in both engagement in care (appointment adherence) and undetectable viral load at 6 months. Depending on appointment adherence and undetectable viral load in the standard of care control group, we will be able to detect a minimum 40% difference, assuming 80% power and type 1 error probability (alpha) = 0.05. Estimates from our study sites suggest that undetectable viral load can be as low as 50% at any given time in our high-risk population. If we observe this level in the standard of care control group at 6 months, we will be able to observe a difference of 40% (or 90% vs. 50%) between the Cohort 1 CAB-RPV LA in the CBOc arm vs. the Cohort 2 CAB-RPV LA in the clinic arm and Cohort 1 CAB-RPV LA in the CBO arm vs. Cohort 3 no CAB-RPV LA arm participants, respectively. Because our intention to treat (ITT) analytic approach may mean an even lower proportion in controls (because missing data will be considered detectable), we believe our sample size is sufficient to yield rigorous clinical outcomes.

11.3 Statistical Methods

We will first conduct exploratory analyses to assess the completeness and distributional properties of all variables, including an exploration of location (e.g., means for continuous variables and frequencies and percentages for categorical variables), spread (e.g., ranges, standard deviations), and shape (e.g., normal, skew). Missing baseline sociodemographic data will be imputed using single or multiple imputation technique if the proportion missing is <10% or ≥10%, respectively. After enrollment, we will compare dropout rates and characteristics of subjects who drop out or are lost to follow-up to assess potential for bias. In cases of missing viral load data, we will treat the result as detectable, in accordance with our primary ITT analytic approach, similar to other studies. Our primary analyses will be by ITT, but we will also conduct per protocol analyses via logistic regression models to estimate treatment effects.

Sociodemographic, behavioral, and clinical attributes at baseline will be compared between Cohort 1 and Cohort 2 and Cohort 1 and Cohort 3 using Chi Square and Fisher Exact test for categorical variables and T-test and Wilcoxon and Kruskal-

Wallis tests for continuous variables. Differences in engagement in care will be examined in two separate models to compare Cohort 1 vs Cohort 2 and Cohort 1 vs. Cohort 3. We will construct a multivariable logistic regression model with a logit link and the events/trials syntax to model the outcome. The inclusion of key baseline variables for adjustment will be based on a p value of ≤0.2 in the bivariate analysis or clinical significance. The following regression equation will be used:

$$Engagement\ in\ care = \alpha + \beta_1 * ixgroup_1 + \beta_2 * factor_1 + \ldots \beta_n * factor_n + \varepsilon,$$

where $ixgroup_1$ is a dummy variable for cohort assignment, α is the intercept, β_1, β_2,…. B_n is a vector of possible coefficients, and ε is an error term**.** Similarly to examine adherence we will use a multivariable logistic regression with a dichotomous outcome for undetectable viral load status at 6 months. Potential confounders will be examined using methods described above and entered into the final model based on a p value of ≤0.2 or clinical significance. We will conduct stratified analyses based on gender and other risk attributes (e.g. homelessness, substance use, etc.), though this will be exploratory, given the cohort study's pilot nature and our sample size.

12. Budget Justification

Our total enrollment into Objective 2 remains 60 participants. Therefore, the resources necessary to accomplish the scope remain unchanged, and we are not requesting a budget increase.

13. Ethics/Protection of Human Subjects

This study will be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines). This protocol and any amendments will be submitted to the Boston Medical Center/Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

14.0 Literature Cited

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