

## Implementation Science Questions for CAB

BioPIC, April 2022

Identifying feasible, affordable strategies for delivering injectable cabotegravir (CAB) is critical to ensuring that it – and other emerging HIV prevention tools – offer greater options to individuals who may benefit from using ARV drugs for prevention and can have an impact on the epidemic. Drawing on country landscaping analyses for CAB for PrEP introduction, [lessons from oral PrEP implementation](#), and a think tank with researchers, implementers and civil society in September 2021, AVAC and partners have identified sample implementation science research questions. Although these questions are focused on CAB for PrEP many are equally relevant for a range of new HIV prevention options (highlighted in blue). Research approaches and outcomes will likely vary by context, population, and other factors, so it will be important to balance large projects to inform and drive scale up with efforts to identify effective strategies for specific populations and geographies.

Implementation research will be adapted to various contexts, but for the most part drive toward similar outcomes. These outcomes evaluate the overall effectiveness of separate (and hopefully cumulative) impact of HIV prevention products on the epidemic, documents actual acceptability, use patterns and challenges in “real world” conditions and compares the effectiveness of different delivery models. Standardizing outcomes across projects and partners can help to produce more comparative and generalizable data and identify what strategies can and should be taken to scale.

### Key Outcomes for CAB Implementation Science Research

Category	Outcomes
<b>Uptake and Adherence</b>	<p>Where feasible, disaggregate outcomes by age and gender:</p> <ul style="list-style-type: none"> <li>• Proportion of eligible individuals initiating CAB</li> <li>• Proportion of new PrEP (PrEP naïve) CAB enrollments versus oral to CAB switches.</li> <li>• Proportion of individuals who seroconvert while using CAB</li> <li>• Proportion of individuals who acquire drug resistant HIV infections due to PrEP exposure v. those you acquire transmitted drug resistance (i.e. NNRTI mutations)</li> <li>• Proportion of individuals who stop using CAB and switch to another prevention method, who stop and use another prevention method to cover the tail, who stop without using another HIV prevention method; reasons for doing so</li> <li>• Reduction in HIV incidence among CAB users; number of HIV infections averted</li> </ul>
<b>Cost-effectiveness</b>	<ul style="list-style-type: none"> <li>• Delivery and commodity costs of CAB</li> <li>• Cost of PrEP delivery by model typology</li> <li>• Cost-effectiveness and cost utility of CAB in different implementation scenarios, including when CAB is prioritized to “high risk” individuals or all individuals who could benefit from PrEP and comparisons to other PrEP options.</li> <li>• Cost-effectiveness of different HIV testing approaches</li> </ul>
<b>Collateral Benefits</b>	<ul style="list-style-type: none"> <li>• Impact of delivering CAB within FP clinics on contraceptive uptake and adherence</li> </ul>

Category	Outcomes
	<ul style="list-style-type: none"> <li>• Impact of use of CAB on STI incidence (i.e. implications of risk compensation)</li> <li>• Impact of CAB availability and use on overall HIV prevention coverage</li> <li>• Impact of delivery of CAB on uptake of a range of primary health care services, including ANC/postnatal care attendance and uptake of SRH services</li> <li>• Feasibility and health facility readiness for CAB implementation</li> </ul>
<b>Community and end user engagement</b>	<ul style="list-style-type: none"> <li>• Increased community awareness and education of CAB as a prevention option</li> <li>• Increased end-user and community participation in CAB implementation research, delivery, monitoring and demand generation</li> <li>• Changes in reported quality of life, depression or anxiety and self-efficacy/empowerment</li> </ul>

**Key Considerations for Implementation Research for CAB**

Clarity and specificity on geographic, population, evidence generation and timeline priorities will help narrow and refine implementation science research questions. Key considerations include:

Category	Considerations
<b>Geographies</b>	Gathering evidence from multiple regions/districts/provinces within a country can help governments understand how delivery approaches might vary based on differences in rural vs. urban; cultural practices; social and economic development; and existing health system variations.
<b>Populations</b>	<p>Evidence across a wide range of populations within a broader “public health approach” will enable governments to make informed decisions during scale-up AND help reduce potential stigma of the product and/or of users (as was seen in some early population-specific oral PrEP programs). Stratifying outcomes by population will be critical to engender a more nuanced understanding of how patterns of use differ across different populations.</p> <p>Additional groups for which we currently lack sufficient data in regard to CAB include:</p> <ul style="list-style-type: none"> <li>- people who use drugs</li> <li>- sex workers</li> <li>- pregnant and breastfeeding women</li> <li>- adolescents below the age of 18 years of age, particularly between 15-18 years an age groups that has struggled with adherence to daily oral PrEP across settings</li> <li>- transgender women given small number of participants in the clinical trials and unknown potential drug-drug interaction between CAB with gender affirming hormone therapy.</li> </ul>
<b>Evidence Generation</b>	Research questions may differ depending on stated priorities: innovation, replicability, sustainability, or other characteristics. It is important to ensure government buy-in for any planned investments as well as for potential scale-up, and this planning will vary depending on whether a given research effort is looking to, for example, investigate innovative models that may be more resource-intensive or those that require the least significant systems changes to operationalize and bring to scale.

Category	Considerations
Timeframe	Project duration can impact the types of questions; for example, longer investments that include a “bridge-to-scale” for early implementation projects should include mechanisms for adaptation, such as the Developmental Evaluation (DE) component used in the Jilinde project to ensure projects are actively evolving based on real-time learnings. <sup>1</sup> Discrete and shorter-term implementation science projects may be more narrowly focused to ensure that they reach clear and actionable conclusions with more discrete questions.

### Key Questions for Implementation Research for CAB

Illustrative questions to guide implementation research for CAB are described below. While some of these questions are very specific to CAB and its attributes, many of these questions are not product-specific and can be applied to other products as well (highlighted in blue). Data on service utilization should be disaggregated by general demographics (age, gender, priority population, urban vs. rural, income, education, etc.), as well as behavioral and knowledge-based characteristics such as experience using oral PrEP, relationship status, and awareness of CAB. Other aspects may also be important to specific user groups or settings.

Given that CAB for PrEP will be introduced alongside and in parallel with other ARV-based options, there is an opportunity to identify barriers and facilitators (e.g., enabling environment, service-delivery, provider-level, and client-level) to initiation and continued use of different PrEP methods (i.e., daily oral, event-driven oral, monthly ring, long-acting injectable, etc.)

Category	Sample Questions
Community linkages	What community mobilization strategies are most preferred and effective at increasing awareness and acceptability of CAB?
	What community-driven interventions are most acceptable and effective at helping to monitor the quality of CAB delivery?
	What models that connect community groups and service providers trained to offer CAB are most effective at meeting the diverse populations’ priorities and needs?
Service Delivery	How can CAB service delivery be integrated with other delivery channels such as STI, FP, ANC/MCH and PHC services?
	What is the impact (collateral benefits or detriment) on STI, FP and PHC services when CAB is integrated?
	Among prioritized service delivery channels (including STI clinics, FP clinics, and drop-in centers) which channels have the broadest reach among priority populations? Does this vary by region or setting in a given country? How do costs compare across these channels?
	How does CAB uptake and patterns of use differ across prioritized delivery channels and priority populations?
	What is the most decentralized and simplified model (for providers and clients) for delivering CAB that is feasible, safe and sustainable?

<sup>1</sup> Fogarty et al. 2020. [Using developmental evaluation to implement an oral pre-exposure prophylaxis \(PrEP\) project in Kenya](#). Gates Open Research.

Category	Sample Questions
	<p>What is the impact on FP coverage of integrating delivery of this product within FP clinics? Are there collateral benefits of integrating CAB delivery with SRH services in FP clinics?</p> <p>What are optimal HIV testing strategies for CAB initiation? Is nucleic acid testing (NAT) necessary, feasible and beneficial prior to initiating CAB? Are 4<sup>th</sup> generation assays an acceptable alternative for detection of acute HIV infection? If NAT is necessary, what is the most affordable and feasible protocol for NAT prior to CAB initiation? What are the implications for cost, wait times, providers and other dimensions of service delivery?</p> <p>What are optimal HIV testing strategies for CAB continuation? What HIV testing is beneficial after CAB discontinuation?</p> <p>What proportion of clients that initiate CAB return on time for follow up injection? What is the average time between scheduled visit and actual follow up visit and are delays associated with HIV acquisition? What are rates of HIV infection and resistance among clients at initiation, receiving CAB on time, receiving CAB with delays and during the tail period? What health systems mechanisms need to be in place to ensure follow-up HIV testing after stopping CAB?</p> <p>What additional service delivery channels are needed to deliver CAB to populations not reached by those prioritized for early rollout? How can these efforts partner with existing community structures and social organizations?</p> <p>How do women using Depo-Provera (injections every 3 months) respond to the additional and asynchronous clinic visits needed to use CAB (injections every 2 months)? What is the impact, if any, on adoption and continuation of product use for depo and CAB? Is switching to NET-EN (injections every 2 months) feasible and acceptable to service providers, health systems and clients? Does doing so have an impact on adoption and continuation of CAB and NET-EN?</p> <p>What client flow and infrastructure changes are needed to infrastructure to ensure privacy for clients receiving injections in the buttocks?</p>
	<p>What practices are in place for safe injections and biohazard waste disposal? How do provider views and capacity around safe injections and biohazard waste disposal affect decisions to offer different PrEP options?</p>
<b>Providers</b>	<p>Is delivering CAB through different healthcare cadres, including nurses, midwives, and community health workers, feasible and acceptable in the country or region? What type of certification and training is required? What is the impact on delivery costs, client uptake and continuation of involving different healthcare cadres at various stages of the client pathway?</p> <p>What training methods are most effective for providers? How does this differ across cadres or by type of provider, e.g. HIV or FP nurse and community health workers?</p> <p>What interventions support empathy building and increase willingness, comfort and safety concerns to offer CAB?</p> <p>What training is required for different types of providers to administer CAB injections in the buttocks? Can CAB injections be administered elsewhere such as the thigh or arm? What are the prospects and requirements for self-injection, and how can implementation research anticipate and inform future prospects for self-injection?</p>

Category	Sample Questions
<b>Demand Generation</b>	What motivates users to choose CAB among different prevention options? What are client views and concerns on taking oral PrEP after stopping CAB? What proportion of clients take oral PrEP after stopping CAB? What are their reasons for doing so?
	What user characteristics and demographics are associated with higher uptake and effective use/continuation of CAB?
	What are preferred demand generation channels among clients (by age, gender, population, location) and which are perceived to be the most reliable sources of information for CAB? Which channels have broadest reach among priority populations? How can community groups be engaged as partners to shape messages and delivery for reach and impact?
	What demand generation channels are associated with the highest rates of uptake and continuation among priority populations?
	What are the costs associated with each demand generation channel?
	How does effectiveness and cost-effectiveness of these demand generation channels compare across priority populations and demographic factors?
	What are the most effective messaging and delivery channels for a “two pronged” approach to create awareness among the general population while providing targeted information to priority user groups?
	What interpersonal messaging on CAB resonates most with users?
	What is the impact of integrating messaging for CAB within existing programs on the uptake of HIV prevention services offered by those programs?
	What are the most effective strategies for engaging key influencers (parents, peers and partners)?
	Given that CAB may not be delivered at the same place where potential users receive information about the product, what are effective approaches for facilitating linkages between information and delivery channels so that interested clients initiate CAB as soon as possible?
	How can the concept of injection for HIV prevention be conveyed clearly to the public and potential users as distinct from vaccination in the context of vaccine hesitancy?
	<b>Effective use support</b>
What counseling and effective use support is particularly effective for individuals who stop taking CAB and still require and want to use an HIV prevention method?	
What counseling messages help individuals to anticipate barriers to effective use and overcome them?	
What mHealth tools, apps and content support effective use?	

**Areas Requiring Further Product Introduction Support & Technical Assistance**

Other areas outside research contexts would benefit from investment, including management, decision-making, and coordination processes and structures, as well as national and sub-national health systems strengthening. Additional product introduction investment across these health system pillars are key to ensuring that implementation science projects can pave the way for efficient, effective, and sustainable product introduction and scale-up.

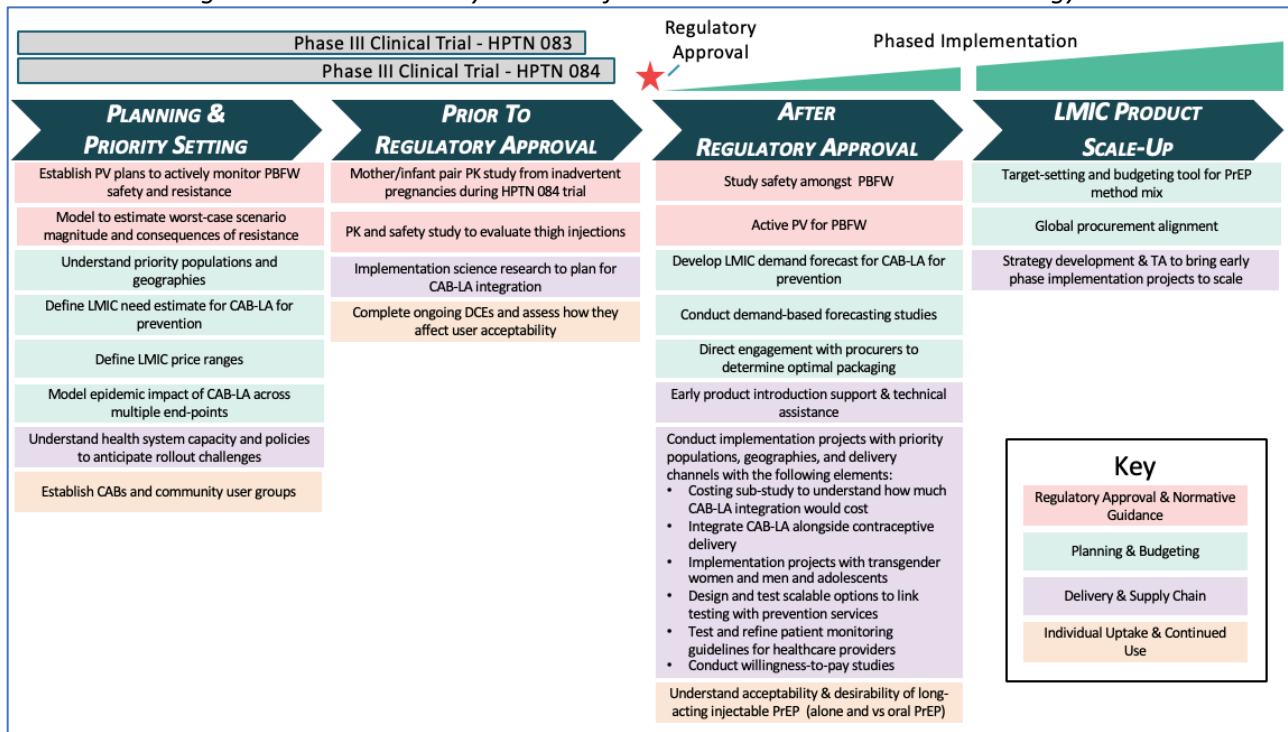
<b>Health Planning, Infrastructure and Governance Questions</b>	
<b>Coordination</b>	What are the optimal mechanisms at the national and sub-national level for coordinating CAB (and other new product) introduction, what stakeholders need to be involved, from which sectors and how can these efforts be sustained? What existing community structures can contribute to the design, delivery and monitoring of CAB introduction?
<b>Supply Chain</b>	How can supply security be effectively integrated into government supply chain systems? What challenges related to forecasting and logistics management arise with introduction of CAB which has different auxiliary supplies and dosing frequency compared to the Dapivirine vaginal ring and oral PrEP introduction? What ongoing support or investment is required to guard against stockouts in each country context?
<b>Laboratory Infrastructure and Resistance Monitoring</b>	What laboratory requirements and changes are needed to ensure timely and high-quality testing results at baseline and follow-up? What birth outcomes and adverse events monitoring systems exist and what adaptations are needed to integrate CAB? What resistance monitoring systems enable timely detection of HIV resistance in the event of breakthrough infections when individuals initiate or are receiving CAB?
<b>Affordability</b>	What will be the willingness-to-pay for CAB among varying priority populations in each country?
<b>Planning and Guidance</b>	How can existing tools and guidance be rapidly updated to accommodate new considerations for CAB?

**Annex – Critical Pathway Activities from BioPIC’s CAB Introduction Strategy**

The Biomedical Prevention Implementation Collaborative (BioPIC) brought together a diverse group of 100+ HIV prevention experts, including representation from all global stakeholder groups such as civil society, donors, researchers, policymakers, normative agencies, program managers and implementers to develop a comprehensive, coordinated product introduction agenda and access strategy to ensure successful and rapid introduction of CAB. The group developed both an initial [CAB Introduction & Access Strategy](#) (May 2020) and an [Adaptable Product Introduction Framework](#) (March 2021).

The following visual outlines the activities that have been identified on the “critical pathway” for product introduction in LMICs.<sup>2</sup> The questions outlined above primarily inform country-level planning for implementation projects and early product introduction support & technical assistance. However, it will be important to ensure country-level activities are effectively linked to the broader CAB product introduction strategy to facilitate alignment and coordination in defining indicators, methodology and outcomes.

*Figure 1. Critical Pathway Activities from BioPIC’s CAB Introduction Strategy*



<sup>2</sup> **Critical Pathway:** refers to activities that are *completely essential* to product introduction. Without a critical activity, the product will not be able to be accessed by clients in low- and middle-income countries (LMIC). For example, if we can reasonably assume that if an activity is not completed the product will not be approved by National Drug Regulatory Authorities (NDRAs), the activity is on the critical pathway for product introduction. This definition differs from activities that are considered “enabling” activities, which serve to optimize delivery and improve impact. Access the full CAB Product Introduction Strategy, with the complete list of critical and “enabling” activities [here](#).