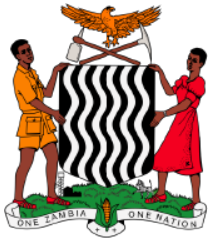
Republic of Zambia
Ministry of Health

IMPLEMENTATION PLAN FOR INTRODUCTION OF LONG-ACTING INJECTABLE CABOTEGRAVIR FOR HIV PREVENTION

November 2023



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for Introduction of Long-Acting Injectable Cabotegravir for HIV Prevention

Directorate of Public Health & Research

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Acronyms

AGYW	Adolescent Girls and Young Women
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AYP	Adolescents and Young People
CAB	Cabotegravir
CAB-LA	Long-Acting Injectable Cabotegravir
CBP	Community-Based Provider
DTG	Dolutegravir
HIV	Human Immunodeficiency Virus
HIVDR	Human Immunodeficiency Virus Drug Resistance
INSTI	Integrase Strand Transfer Inhibitor
MoH	Ministry of Health
MVP	Most Vulnerable Populations
NAC	National HIV/AIDS/STI/TB Council
NASF	National HIV and AIDS Strategic Framework
PEPFAR	The U.S. President's Emergency Plan for AIDS Relief
PK	Pharmacokinetics
PrEP	Pre-Exposure Prophylaxis
QA	Quality Assurance
QI	Quality Improvement
STI	Sexually Transmitted Infection
TDF/FTC	Tenofovir Disoproxil Fumarate/Emtricitabine
TWG	Technical Working Group
WHO	World Health Organization
ZAMRA	Zambia Medicines Regulatory Authority

Foreword

It is with great pleasure and a profound sense of purpose that we introduce the "Implementation Plan for Introduction of Long-Acting Injectable Cabotegravir (CAB-LA) for HIV Prevention." This plan is the result of a collective endeavor, spearheaded by the Ministry of Health (MoH) Directorate of Public Health and Research, with the invaluable contributions of various institutions and experts.

The urgency of our mission is underscored by the 2021 Zambia Population-based HIV/AIDS Impact Assessment report, which revealed a significant annual incidence of HIV among adults aged 15+ years in Zambia. To effectively combat this ongoing challenge, we recognize the imperative need for innovative prevention strategies. Pre-Exposure Prophylaxis (PrEP) stands as a critical component of our comprehensive HIV prevention approach. The World Health Organization (WHO) has endorsed oral PrEP for individuals at substantial risk of HIV. However, it is evident that certain vulnerable groups, such as Adolescent Girls and Young Women (AGYW), face barriers that result in low persistence in the use of oral PrEP in sub-Saharan Africa.

The clarion call of the WHO endorsing CAB-LA as an additional prevention option resounded across the globe. This plan serves as our response to that call, as we embark on an innovative approach aimed at curbing the transmission rates of HIV. Cabotegravir presents and offers an alternative to the daily regimen of oral PrEP, offering the promise of enhanced adherence and efficacy. In this plan, you will find a meticulous roadmap outlining our systematic approach to implementing CAB-LA PrEP, with unwavering attention to its efficacy, safety, acceptability, and the challenges we may encounter along the way.

This plan has been made possible through the unwavering support and collaboration of research institutions, healthcare facilities, Non-Governmental Organizations (NGOs), Community-Based Organizations (CBOs), international partners, and generous donors. It is a testament to the dedication and resilience of our healthcare professionals and frontline workers, who have tirelessly championed the successful implementation of oral PrEP in Zambia and the expansion of access to public health facilities.

The "Implementation Plan for Introduction of CAB-LA for HIV Prevention" is not merely a document; it is a testament to our unwavering commitment to combat HIV and enhance the overall health outcomes of our beloved nation. Acknowledging the challenges posed by HIV resistance to Integrase Strand Transfer Inhibitors (INSTIs), we pledge to exercise utmost diligence in devising strategies to mitigate such risks.

To all those who have contributed to shaping this plan, we extend our heartfelt appreciation. We stand united in our resolve to work hand in hand, pursuing the noble vision of an HIV-free Zambia. Together, we shall transform this vision into reality, ensuring a healthier and brighter future for our people.

Dr. George Sinyangwe

Permanent Secretary – DC

Ministry of Health

Acknowledgements

The "Implementation Plan for Introduction of CAB-LA for HIV Prevention" is a collaborative effort led by the MoH Directorate of Public Health and Research. It incorporates expertise from health facilities, NGOs, and CBOs, and funding from international partners and donors. The plan aims to introduce long-acting injectable cabotegravir to prevent HIV transmission and improve overall health outcomes. This comprehensive approach reflects the commitment of all involved in combating HIV and enhancing public health. The Ministry of Health would like to extend its appreciation and thanks in particular to the following organizations.

National HIV/AIDS/STI/TB Council (NAC)
World Health Organization (WHO)
United States President's Emergency Plan for AIDS Relief (PEPFAR)
United States Agency for International Development (USAID)
Center for Disease Control (CDC)
University of Maryland Baltimore (UMB)
Ciheb Zambia
Centre for Infectious Disease Research in Zambia (CIDRZ)
Clinton Health Access Initiative (CHAI)
Maximizing Options to Advance Informed Choice for HIV Prevention (MOSAIC)
USAID Action to Epidemic Control of HIV (USAID ACTION-HIV)
USAID Controlling HIV Epidemic for Key and Underserved Populations (CHEKUP II)

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Background

According to the 2021 Zambia Population-based HIV/AIDS Impact Assessment report, annual incidence of HIV among adults aged 15+ years in Zambia is 0.31%, which corresponds to approximately 28,000 new cases of HIV per year among adults. HIV prevention is a cornerstone of HIV epidemic control. Pre-Exposure Prophylaxis (PrEP) for HIV prevention is a key component of combination HIV prevention and has the potential to significantly reduce HIV incidence. In 2015 the World Health Organization (WHO) recommended oral PrEP containing Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) for people at substantial risk of HIV. However, studies on the use of oral PrEP in Sub-Saharan Africa have shown low persistence among some groups, including Adolescent Girls and Young Women (AGYW) who are among the most vulnerable to new infections.[1,2] Hence, there is substantial interest in other forms of PrEP that do not require a daily pill. Potential barriers to the uptake and effective use of oral PrEP, such as not wanting to take an oral pill regularly, may be overcome with a long-acting injectable option.

Implementation of Oral PrEP in Zambia

Oral PrEP was introduced in Zambia in 2017 with a pilot study in Lusaka and Livingstone. Successful implementation led to the inclusion of PrEP in national HIV guidelines in 2018 and the formation of a national task force consisting of the Ministry of Health (MoH), the National HIV/AIDS/STI/TB Council (NAC), World Health Organization, donors, Civil Society representatives, and PEPFAR implementing partners. At the end of 2020, access to oral PrEP had expanded to 906 public health facilities. While oral PrEP is largely provided in ART clinics, facilities have started to provide information and referrals for oral PrEP within family planning services and youth-friendly spaces as well as further differentiation to community-based service provision, including DREAMS centers targeting adolescent girls and young women.[3] A rapid assessment in 2020 found high acceptability and desire to access oral PrEP; however, the greatest challenge is continuation of oral PrEP.[4]

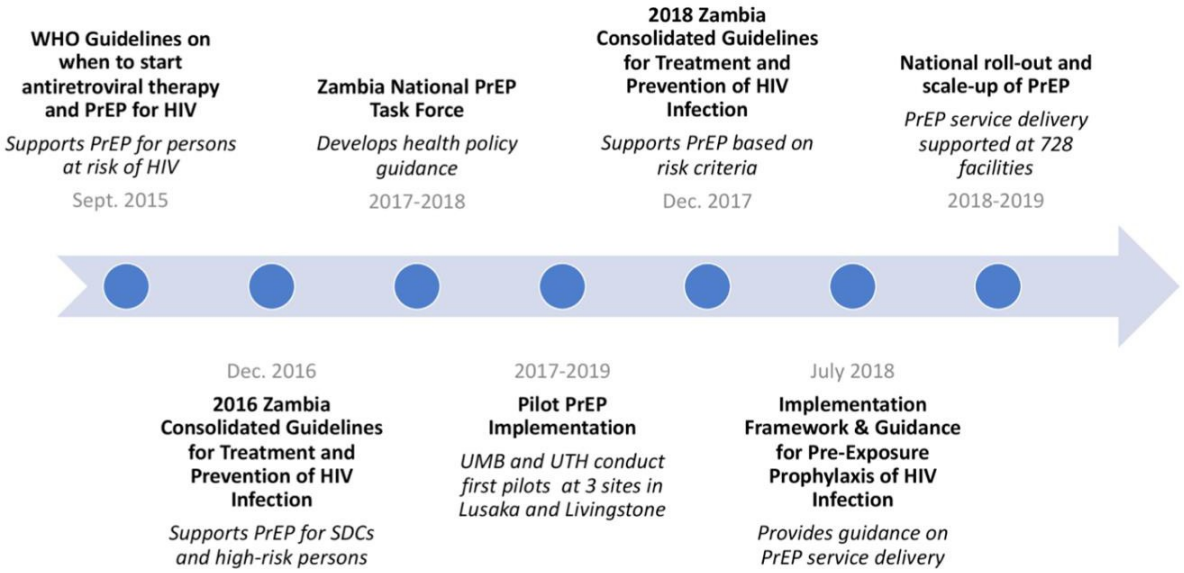

Figure 1: Oral PrEP Introduction in Zambia

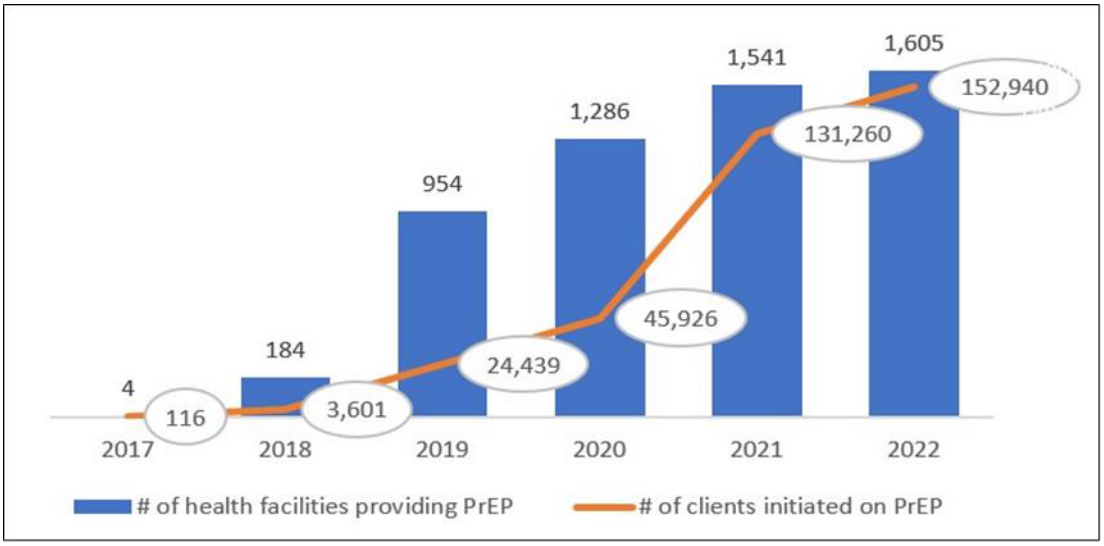

Figure 2: Trends in Access to Oral PrEP in Zambia (2017 – 2023)

Global Guidance on CAB-LA for HIV Prevention

In 2022, the World Health Organization recommended that CAB-LA may be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches.[5] Cabotegravir is an INSTI, an antiretroviral (ARV) in the same family as Dolutegravir (DTG), which is currently part of the recommended first-line ART regimen in Zambia.[6] Cabotegravir can be given either as a pill or an injection; when given as an injection, it is known as long-acting Cabotegravir. Cabotegravir can either be used for treatment of HIV in combination with other ARVs or on its own as PrEP. When used as PrEP, it is given as an intramuscular injection with the first dose at initiation, the second dose at four weeks thereafter, additional doses of CAB-LA are administered at 8-week intervals.[7]

Efficacy

Long-acting injectable Cabotegravir was shown to be statistically superior to daily oral TDF/FTC in preventing HIV acquisition when administered every eight weeks among cisgender men, transgender women, and people assigned female at birth who were mostly cisgender women, in two large clinical trials. HPTN 083, a Phase 2B/3 double blind study, among cisgender men and transgender women in the United States, Latin America, Asia, and Africa found a 66% reduction in risk of HIV acquisition as compared to oral PrEP.[8] In HPTN 084, a Phase 3 double blind study among people assigned female at birth in sub-Saharan Africa, participants in the CAB-LA PrEP arm were found to have an 88% reduction in risk of HIV acquisition as compared to the oral TDF/FTC arm.[9]

Safety Profile

Two Phase 3 clinical trials (HPTN 083, HPTN 084) established that Cabotegravir administered every eight weeks for HIV prevention was well-tolerated among cisgender men, transgender women, and people assigned female at birth in East and Southern Africa. Injection Site Reactions (ISR) were usually mild, associated with pain, and typically occurred after the first injection.

Acceptability

Ongoing research regarding the acceptability of Cabotegravir across Africa includes three studies, HPTN 083, HPTN 084, and HPTN 084-01, a sub-study of HPTN 084.

Advantages & Disadvantages

There are both advantages and disadvantages of Cabotegravir as PrEP (Table 1). The superior protection provided by Cabotegravir is likely due to higher adherence, as CAB-LA PrEP requires an injection every two months whereas oral TDF/FTC requires a daily pill. A potential drawback of CAB-LA PrEP is the long pharmacokinetic (PK) half-life, resulting in a 'tail.' During this tail phase, Cabotegravir drug levels are not sufficient to prevent viral replication despite the drug being present (Figure 3). If a client on CAB-LA PrEP acquires an HIV infection during this tail period, it could lead to HIV resistance to INSTIs as a class; this includes potential resistance to DTG, the current first line ARV.

Table 1: Advantages and Disadvantages of CAB-LA

Advantages	Disadvantages
▪ May address adherence issues due to the less frequent dosing schedule ▪ May be preferred for patients who wish to avoid burden or stigma of daily oral antiretrovirals ▪ Fewer (or different) side effects ▪ Lower overall drug dose ▪ High acceptability and patient satisfaction	▪ Frequent clinic visits may be resource-intensive and pose a barrier to adherence ▪ Potential long-lasting side effects ▪ High dosing volumes may result in painful injection site reactions ▪ Some people may not like injections ▪ Potentially very high cost ▪ Potential for resistance in non-adherent patients ▪ Lack of safety data in pregnancy ▪ Contraindication for patients with co-infections (e.g., Hepatitis B, Tuberculosis)

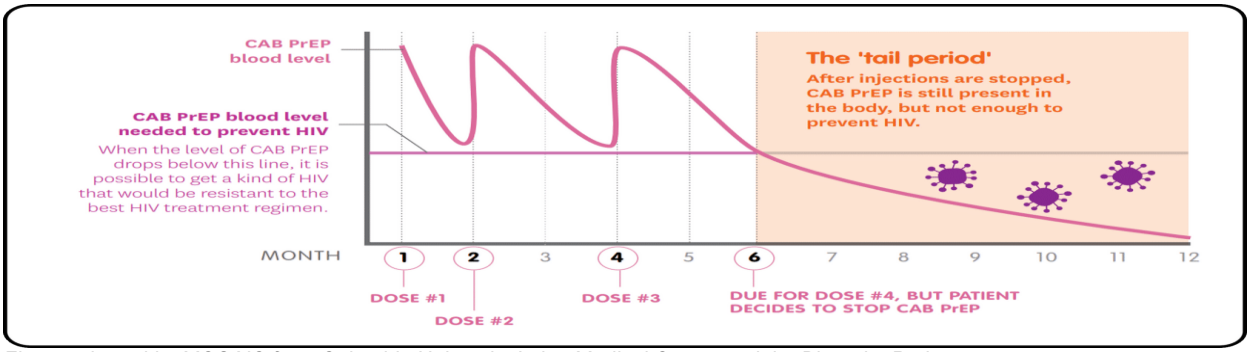

Figure adapted by MOSAIC from Columbia University Irving Medical Center and the Blueprint Project

Figure 3: Pharmacokinetics of CAB-LA PrEP with extended PK Tail

Introduction of CAB-LA for HIV Prevention

In early 2023, Zambia was among five countries to receive a donation of CAB-LA from the US Government through the President's Emergency Plan for AIDS Relief (PEPFAR). The Ministry of Health anticipates receiving 42,500 vials of CAB-LA to support 6,000 individuals from October 2023 to September 2024. To guide CAB-LA PrEP implementation and learn lessons for future scale-up, the Ministry of Health has recommended a phased approach, with the initial target population being HIV-negative individuals older than 16 years and most vulnerable populations.

CAB-LA PrEP increases the options available and should always be offered alongside oral PrEP. Some people may continue to choose oral PrEP; CAB-LA PrEP will likely be preferred by people who find it difficult to take tablets or do not want to do so.[17]

Value Chain Situation Analysis

In 2022, Maximizing Options to Advance Informed Choice for HIV prevention (MOSAIC) conducted a value chain situation analysis to identify critical steps for the introduction of biomedical HIV prevention products. Inputs to this analysis included a desk review, secondary research, and interviews with key stakeholders in Zambia. The key findings were:

- High demand for CAB-LA PrEP and people already asking for the injectable as an alternative to the pill
- The success of CAB-LA PrEP roll-out will depend on a well-coordinated mechanism between stakeholders
- Leveraging existing oral PrEP service delivery channels will be key to reach end users.
- Need for gender mainstreaming of PrEP at a national level
- A key obstacle around CAB-LA PrEP is the estimated high cost of the product

The value chain situation analysis identified some strengths and barriers across the priority delivery channels (Table 2).

Table 2: Strengths and Barriers across Priority Delivery Channels

Category	Strengths	Barriers & Gaps
Planning and budgeting	▪ National TWG recommended to move forward with CAB-LA PrEP introduction ▪ Following PEPFAR decision to procure CAB-LA for Zambia ignited policy guidance on introduction and implementation ▪ Framework for clinical guidelines available	▪ CAB-LA not yet registered in Zambia ▪ Limited quantities of CAB-LA committed
Supply chain management	▪ CAB-LA included in the national procurement plan ▪ Capacity of MoH to set national targets using PrEP-It tools to support forecasting and quantification of PrEP commodities ▪ Strong partnerships with supply chain management	▪ High oral PrEP discontinuation rates were linked to medication and test kit stock outs ▪ Inadequate subnational oral PrEP data reduced accuracy of the PrEP-It tool target estimates
Service delivery platforms	▪ Best practices learned from oral PrEP regarding delivery models ▪ Private sector model explored (Mines) ▪ Leverage oral PrEP training curriculum, tools and job aids for adaptation ▪ Availability of implementing partners with experience in PrEP service provision	▪ Need strong social and behavior change programs to support demand creation through nontraditional channels: FBOs, community, private sector ▪ Integration into SRH may be challenging because PrEP medication is an ARV which may raise misconceptions and stigma around target audience's HIV status ▪ Private sector landscape analysis is needed to support CAB-LA PrEP introduction ▪ Age of access for AGYW may be a barrier to integration within AYP services
Uptake and effective use	▪ Availability of testing and counseling services in all public and private facilities ▪ Trained providers in PrEP provision ▪ Implementation structures at all levels to support service provision	▪ Outdated HIV prevention and communication strategy ▪ National training materials for CAB-LA PrEP not available ▪ Inadequate QA/QI systems
Monitoring and evaluation	▪ Updated national M&E framework and monitoring tools	▪ Inadequate capacity/systems to monitor HIVDR ▪ Inadequate capacity of IPs to collect PrEP continuation data country wide

Implementation Approach

Purpose

To guide service delivery of CAB-LA PrEP as an additional biomedical prevention choice for people at substantial risk of HIV infection and as part of the combination HIV prevention approaches.

Goals

To assess feasibility, acceptability, uptake, and patterns of use of CAB-LA PrEP among HIV-negative high-risk individuals aged 16 and older, focusing on intersectionality with most vulnerable populations established health facilities and community PrEP sites with robust data management and community tracking systems.

Objectives

- To characterize the implementation effectiveness of CAB-LA PrEP and its parameters.
- To establish the feasibility, and acceptability of CAB-LA PrEP in Zambia.
- To learn lessons and implementation models based on evidence.

Guiding Principles

The goal of this framework is to provide guidance on the strategic direction to achieve results within a specific time and accelerate impact with the introduction of CAB-LA for PrEP. This implementation strategy will focus on the specific principles for CAB-LA PrEP introduction and align with national frameworks, including Zambia National Consolidated Guidelines for HIV Treatment and Prevention, Zambia National PrEP Implementation Framework, Zambia Differentiated Service Delivery Implementation Framework, and the PrEP M&E Implementation Guideline.

- Leadership and accountability at all levels
- Accelerate scale and speed
- Deliver impact
- Center the community and user
- Work with what we know while constantly adding to the evidence base
- Lead with equity
- Ensure safety of beneficiaries

Ministry of Health Guidance for Initial Implementation Phase

A phased approach to implementation will ensure that lessons learned in the initial implementation phase are incorporated in the later expansion and scale-up phases. The initial implementation phase should be conducted in Southern province (Mazabuka), Lusaka province (University Teaching Hospital), Central province (Chibombo), and Copperbelt province (Kitwe). The selected population includes adolescents and young people (16 to 24 years) comprised of 80% adolescent girls and young women and 20% adolescent boys and young men. Intersectionality where possible may include most vulnerable populations (MVP) at substantial risk of HIV infection. The population should include those aged 16 years of age and above at risk of HIV acquisition and anticipates being on PrEP for the coming 12 months. Fifty percent must have demonstrated adherence for more than six months on oral PrEP, whereas the other 50% should be new initiators on PrEP.

Protocol for Initial Implementation Phase

The initial implementation phase will last one year and will assess the feasibility, acceptability, acceptance, and patterns of usage of CAB-LA PrEP among HIV-negative high-risk individuals. This phase will require planning and preparation of the facilities to introduce the new product. This will involve selection of sites using set criteria, facilitation of national approvals, securing commitments for funds and commodities, target setting and quantification, development of clinical guidelines, developing/adapting training materials, job aids and tools and training of health care providers and selection of implementing partners. The demonstration project will initially be set up and implemented in five districts namely Mazabuka, Lusaka, Chibombo, Kitwe, and Nakonde. These districts were selected based on the previous experience implementing PrEP services, robust M&E system, and active community tracking systems.

The implementing partners participating in the CAB-LA PrEP initial implementation phase should have a demonstrated medical/technical capacity and expertise; prior history of PrEP implementation in Zambia; access and current partnerships/working with health facilities providing PrEP services and with youth-friendly services; demonstrated capacity to generate evidence and disseminate best practices and lessons learned; and ability to fund implementation of activities related to service delivery.

Table 3: Proposed Sites for CAB-LA PrEP Initial Implementation Phase

Site	District	Implementer	Focus
University Teaching Hospital	Lusaka	University Teaching Hospital	Oversight
Matero Main Health Centre	Lusaka	CIDRZ	MVP
Mazabuka DREAMS Centres	Mazabuka	The University of Maryland, Baltimore-MGIC Zambia	AGYW
Kitwe Hub	Kitwe	JSI DISCOVER-Health	AGYW/MVP
Mwanjuni Health Centre	Chibombo	JSI DISCOVER-Health	AGYW/MVP
Nakonde Urban Clinic	Nakonde	JSH CHEKUP II	MVP

Table 4: Selection Criteria

Target Populations	▪ High-risk individuals aged 16 and older ▪ Adolescent girls and young women (80%) ▪ Adolescent boys and young men (20%) ▪ Intersectionality where possible with most vulnerable populations
Inclusion Criteria	▪ 16 years of age and above, with a focus on AYP ▪ At risk of HIV acquisition, and anticipates being on PrEP for the coming 12 months ▪ Agrees to be contacted considering critical need for client tracking throughout time on CAB-LA PrEP and 1 year thereafter ▪ 50% with demonstrated PrEP adherence (≥6 months on oral PrEP) ▪ 50% as new initiators on PrEP
Exclusion Criteria	▪ Currently pregnant or states intent to become pregnant in the next year/currently breastfeeding ▪ <16 years old
Site Selection Criteria	▪ Public sector sites ▪ Experienced staff qualified to conduct this project ▪ Adequate technical skill level (i.e., dedicated study nurse or CO) ▪ High burden district ▪ Adequate data systems for reporting ▪ Mix of different populations, rural/urban sites ▪ Availability of optimum drug storage facility to ensure temperature below 30 degrees Celsius

Statistical Analysis

As part of the analysis, we will conduct univariate analysis to describe the frequency and distribution of outcomes of interest and covariates. Client characteristics will be summarized using means and standard deviations, or medians and Interquartile Ranges (IQR) for continuous variables and proportions with 95% Confidence Intervals (CIs) for categorical variables. We will assess factors associated with our outcomes of interest (on-time injections) using generalized linear mixed models (GLMM).

Expansion Phase

Informed by the findings from the initial implementation phase, more sites will be established to meet the needs of an increased number of individuals targeted to access the drug from 6,000 to 12,000. This phase will expand inclusion of other populations and additional sites. The number of implementing partners will also be increased to replicate the initial sites expanding and building on lessons learned. The expansion phase is expected to start after completion of the initial implementation phase. In preparation for this phase, rollout scenarios will be conducted to inform decision-making for expansion. Different rollout scenarios will identify the different populations and geographic regions most critical to include to ensure greatest impact of CAB-LA PrEP introduction on the HIV epidemic in Zambia.[17]

Scale-up Phase

The Scale-up Phase will commence after completion of the initial and expansion phases. This will be a period of scale-up to all provinces of the country. At least one site providing CAB-LA PrEP will be established in each province. The expansion will be accompanied by increased commitment for procurement and management of commodities, increased program support, systems development, and human resources capacity building interventions.

Table 5: Expected CAB-LA PrEP Outcomes

Eligibility	• Number of clients screened for CAB-LA PrEP who are eligible • Number ineligible clients and reasons why
Uptake	Number of clients who select and initiate CAB-LA PrEP among individuals who are eligible
Persistence	Number of clients who start CAB-LA PrEP who return at 1, 3, 5, 7, 9, 11 months within +/- 7 days window of the scheduled injection
Fidelity	Plan to collect information on how CAB-LA PrEP is implemented at the site for fidelity with national/international guidelines using a checklist and field notes
Acceptability (Adapted from TFA scale12)	▪ How much do you like CAB-LA PrEP? ▪ How comfortable are you with CAB-LA injections? ▪ How much effort did it take on your part to get CAB-LA PrEP? ▪ How much do you think CAB-LA PrEP has protected you from HIV? ▪ How well do you think taking CAB-LA PrEP will work to prevent HIV? ▪ How confident do you feel in your ability to use CAB-LA PrEP as prescribed by your healthcare provider?
Tolerability	Number of clients who discontinue CAB-LA PrEP due to side effects, dislike of going to the clinic, etc. and switch to a different prevention method
Discontinuation	Number of clients who are lost-to-follow-up or discontinue (include reasons for discontinuation)
Adverse Events	Injection site reactions and medication side effects
Seroconversion	Number of clients whose HIV status change from negative to positive while using CAB-LA PrEP
HIV risk at each visit	Self-perception of HIV risk
Services delivery models	Clinical, community-based, etc.
Independent variables	Age, sex, education, etc.

Essential Health Systems for Implementation

Governance and Coordination

The MoH, as the custodian of health in Zambia, coordinates implementation of health service delivery including PrEP as an additional prevention choice for people at substantial risk of HIV infection; and as recommended in the Zambia Consolidated HIV Prevention and Treatment Guidelines and the National HIV and AIDS Strategic Framework 2017- 2021 (NASF). As a sub-committee of the Integrated HIV Technical Working Group, the National PrEP Task Force, coordinated by the National HIV/AIDS/STI/TB Council (NAC), is mandated to oversee, and monitor implementation.

Demand Creation and User Support Recommendations

- Greater community-level PrEP sensitization and information efforts utilizing a range of channels and starting with key influencers, particularly community and traditional leaders, to have rapid buy-in at the community level prior to product introduction or scale-up
- Segment audiences to determine best message content and channel, particularly men (as partners and end users) and most vulnerable populations. Ensure key influencers are included, particularly parents/caregivers and men, as these groups had low PrEP awareness and were identified as important sources of support for HIV prevention method use by end users.[2]
- Promote interpersonal communication with the PrEP recipients through one-on-one interaction with health care providers and peers to share information
- Develop standard operating procedures for healthcare providers and resources for clients which can be used across settings to enhance knowledge on CAB-LA PrEP
- Develop community literacy materials for community leaders, parents, and other key influencers to familiarize communities in initial implementation phase facility catchment areas with the concept of CAB-LA PrEP, CAB-LA PrEP vs. Oral PrEP, and the plans for introduction.[12]
- Develop a robust screening tool for TB, STIs, and Hepatitis B

Medicines and Medical Supplies

Supply chain management is key to the success of the CAB-LA PrEP introduction and implementation. The Ministry of Health has capacity to quantify and forecast for PrEP commodities through the Supply Chain TWG under the leadership of the Supply Chain Management core team referred to as the “Control Tower”.

- Other commodities required for CAB-LA services such as consumables, HIV test kits, pregnancy test kits, and other supplies should be planned for and made available at the demonstration facilities without “stock outs”
- Guaranteed supply of CAB-LA
- Guaranteed supply of consumables (swabs, syringes, test kits, etc.)
- Health systems considerations
- A full bill of material is required to ensure that consumable products are fully quantified for

- CAB-LA to be entered on to the ZAMMSA Warehouse Management System to allow it to be ordered and stock managed
- ZAMMSA to be requested to provide all consumable items to ensure that the CAB-LA "Kits" can be prepacked before being sent to the demonstration sites
- A distribution list to be developed for each demonstration site to ensure that a one-off distribution is completed and the CAB-LA is at the facilities to ensure continual supply
- Each demonstration site to order their allocated quantity of kits for the entire exercise
- Monthly inventory checks at each of the demonstration sites to ensure that inventory accountability is assured

The following commodities and supplies should be planned for and made available at the initial implementation phase facilities:

Table 6: Commodities and Supplies

Long-Acting Injectable Cabotegravir	600mg (3mL) vials
HIV Test Kits	Determine HIV test
	Bioline HIV test
	HIV nucleic acid tests
HIV drug Resistance Testing	HIV drug resistance reagents
Test Kits for STIs and HBV	HBsAg, RPR, LFTs
Pregnancy Test Kits	Gravindex
Supplies & Consumables	5 ml syringe
	23-gauge, 1.5-inch injection needle
	21-gauge, 1.5-inch injection needle
	Non-sterile gloves
	Alcohol wipes
	Gauze pads
	Sharps container

Service Delivery

The implementation of CAB-LA PrEP will deliver PrEP choice between oral PrEP and CAB-LA PrEP for public health service delivery sites, building on the existing PrEP service delivery models at each site and in accordance with national guidelines for PrEP service delivery in Zambia. Since none of the study sites currently offer choice across multiple PrEP products, implementation will enhance service delivery package that supports fully informed user choice between oral PrEP and CAB-LA PrEP. The enhanced service package will include components at the individual, provider, facility and community levels.

Human Resources

The Ministry of Health, with the support of stakeholders, will build capacity of healthcare providers for CAB-LA PrEP services. Training of healthcare providers must include HIV prevention options, behavioral and clinical assessment, laboratory testing, supplies and consumables, comprehensive services, correct administration of CAB-LA, systems and procedures for recording and monitoring PrEP use; ART; CAB-LA PrEP administration; drug resistance; drug-drug interactions; management of chronic hepatitis B infection and sexually transmitted infections,

contraceptive services, and harm reduction services for people who use drugs; and appropriate referral pathways to ensure that specific needs of PrEP users are adequately provided. Healthcare providers should also be trained to detect acute HIV infection in people who report having engaged in exposure-prone activities in the four weeks preceding their PrEP eligibility. Similarly, providers should know how to transition clients who may seroconvert whilst on PrEP to full Antiretroviral treatment.

Pharmacovigilance, Safety and Monitoring

Pharmacovigilance (PV) is the science and activities relating to assessment, detection, understanding and prevention of adverse effects following the use of a drug or any other drug-related problem. It is imperative to strengthen the national pharmacovigilance systems to monitor the tolerability, and Adverse Drug Reactions (ADRs) of new ARVs such as the CAB-LA.

Program teams should adopt active PV monitoring at the facility level and routine monitoring at the national surveillance level. Routine ADR monitoring, also known as passive PV, is already integrated into the monitoring and evaluation of national HIV treatment programs using existing patient-monitoring tools and ART reporting systems.

Active PV monitoring at the facility level will be employed to increase identification, management, and reporting of ADRs, including mild ones. The proposed active PV is a system in which measures are taken to detect the presence or absence of ADRs through specifically designed tools as has been the case with other newer drugs such as DTG.

Zambia Medicines Regulatory Authority (ZAMRA) National Pharmacovigilance Unit (NPVU) has put in place a national guideline for the detection and reporting adverse drug or vaccine reaction and events in Zambia for any prescription medicines and vaccines including ARVs through pharmacovigilance. This will support active PV of newer ARVs, especially CAB-LA, with a focus on collecting and responding to short-term data on its tolerability, and clinically symptomatic ADRs among the PrEP clients, followed by long-term monitoring for other significant ADRs. Early recognition and management of ADRs can improve ART adherence and treatment outcomes. Short-term ADRs are those that may occur in the immediate post–ARV initiation/transition, and long-term ADRs are those that may occur after the first six months post–ARV initiation/ transition.

For all PrEP products used in Zambia, safety monitoring will be followed including reporting on the national adverse drug reaction (ADR) form from the national pharmacovigilance team. Refresher training on the national reporting of adverse drug reactions will be conducted by staff. Healthcare providers will be trained to actively inquire about ADRs during the implementation. All ADRs will be reported back to the national pharmacovigilance team. Monitoring of ADRs frequently involves a clinical assessment, which incorporates the overall ADR profile of the product, including both symptomatic side effects and asymptomatic laboratory, radiographic, and clinical events.

All enrolled clients who seroconvert while on CAB-LA PrEP will be provided with post-test HIV counseling and be initiated on ART as per national guidelines. All seroconverts must receive INSTI resistance testing and provide an opportunity to adjust ART regimen if needed. The results of the HIV Drug Resistance (HIVDR) test will be returned to the facility for communication to the client as per routine MOH procedures. In addition, we will document data on Serious Adverse Events (SAEs) and social harms for all clients including product-related and non-product-related events.

Although pregnancy testing is not required for oral PrEP use in Zambia, pregnant and lactating women will be excluded from being enrolled on CAB-LA PrEP. Pregnancy status of women will be assessed and documented for all women to be initiated/transitioned to CAB-LA PrEP.

Monitoring of Adverse Drug Reactions and Adverse Drug Events

To ensure that close attention is paid to pharmacovigilance activities, all initial implementation sites for CAB-LA PrEP will have their healthcare providers including pharmacists trained on pharmacovigilance tracking and reporting as well as the use of the ADR Screening Forms. These forms will be printed and made available for use at the points of service. Therefore, while rolling out CAB-LA PrEP, emphasis will be placed on ensuring that at each clinical follow-up visits, clients will be screened for basic signs and symptoms of ADRs and ADEs. Based on what is shared by the clients, the HCWs will order relevant laboratory investigations to ascertain if there's incidence of ADR or not.

The ADR Screening Form will use a scoring or grading method to make the screening more objective. Each client screened will be observed and scored by both a clinician and pharmacist. A 4-grade system – 1,2,3, and 4 will be adopted as follows:

- Grade 1: Mild Transient or mild discomfort, no limitation of activity, no medical intervention/therapy required
- Grade 2: Moderate Mild to moderate limitation in activity, some assistance may be needed, no or minimal medical intervention therapy required
- Grade 3: Severe Marked limitation in activity, some assistance usually required, medical intervention/therapy required, hospitalization possible
- Grade 4: Life-threatening Extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization and hospice care
- In addition, we will be documenting data on Serious Adverse Events (SAEs) and social harms for all clients including product-related and non-product-related events

Re-introducing and/or Integration of Tools for Pharmacovigilance in Facilities

The program will print and distribute the finalized ADRs Screening tools and NPVU ADVREF to all demonstration sites and ensure that the Healthcare Workers are responsive to making national pharmacovigilance reporting system active especially between to healthcare facility and national levels. Using Technical Supportive Supervision (TSS) through mentorship support visit to sites, MOH and other partners will help in strengthening and improve the institutionalization of PV screening and reporting system.

Approaches to Mitigating Risk of Integrase (including DTG) Resistance

To mitigate the risk of integrase (including DTG) resistance observe the following:

- Emphasize consistent and correct usage of CAB-LA PrEP, with timely injections and precautions during the "tail" period after discontinuation
- Understand that HIV drug resistance cannot occur in non-HIV individuals, reinforcing prevention methods for this group
- If a planned injection visit is missed by 8 weeks or more (i.e., 16 weeks after the previous dose), then the next 2 injections should be administered 4 weeks apart before returning to a bimonthly injection schedule
    - Conduct the routine checks for possible acute HIV infection for patients that have missed their appointments
- Ensure safe discontinuation of CAB-LA PrEP through patient re-education, risk assessment, and provision of alternative prevention options if necessary
    - Re-educate patients about the “tail” and the risks during declining CAB-LA levels
    - Assess ongoing risk/indications
    - If PrEP is indicated, prescribe daily oral TDF/FTC beginning within 8 weeks after last injection
    - Educate about non-occupational Post Exposure Prophylaxis (nPEP)
    - Continue follow-up visits quarterly for 12 months
    - Conduct HIV-1 RNA tests at each quarterly follow-up visit after discontinuing CAB-LA injections
- Monitor seroconverters for HIVDR, initiate immediate ART based on guidelines, and conduct regular HIVDR laboratory testing to detect and address INSTI resistance
    - All seroconverters will be monitored for HIVDR, with a sample taken at the time of their first HIV positive test
    - These individuals will initiate ART immediately, as per country guidelines, and HIVDR laboratory testing will be conducted to monitor for INSTI resistance
    - Summaries of HIVDR result data will be periodically assessed to identify any potential trends that may impact first line treatment recommendations; and individual results will be provided to the health facility that collected the sample to review with the client and their ART clinician to determine any potential changes needed to their ART regimen

Monitoring, Evaluation and Learning

Introduction of CAB-LA PrEP in Zambia requires Monitoring, Evaluation, and Learning (MEL) of additional elements relative to the existing process for Oral PrEP since a new ARV product is being introduced. This will include both clinical and non-clinical parameters. From this process, PrEP managers and policy makers will be able to learn about internal and external factors unique to Zambian contexts that may either enhance or impede the uptake of and retention on CAB-LA PrEP amongst the client populations during the pilot-implementation. In addition, information gathered from the phased implementation may be useful in guiding the scale-up of CAB-LA PrEP and ensuring that good policies are developed to guide future scale-up.

Preparations for Data Collection and Reporting

To ensure that all participating pilot sites in Zambia are collecting and reporting the same information and data around the CAB-LA PrEP implementation roll-out, the M&E sub-committee of the National PrEP Task Force will develop for adoption a set of M&E data collection tools, ad-hoc indicators, and, in addition, refine the existing national MoH PrEP tools to ensure that it captures salient clinical and non-clinical monitoring data elements around the CAB-LA PrEP being an option for PrEP service delivery in Zambia.

Development of M&E Data Collection Tool and Ad-hoc Indicators

Since the design for CAB-LA PrEP initial implementation phase in each participating site is to recruit 50% new and 50% existing oral PrEP clients who are retained in care, a thorough assessment of all current oral PrEP clients who desire to transition should be conducted in line with the agreed standard criteria. Therefore, a **standardized PrEP transition screening form** will be developed for use to determine that any existing clients being transitioned from daily oral PrEP to CAB-LA PrEP meet the standard criteria in terms of the required combination of the level of adherence and other clinical and non-clinical parameters agreed upon. Upon transitioning to CAB-LA PrEP, the tools being used for client's clinical consultation – i.e., PrEP initial and PrEP follow-up forms need to be updated and refined to include any clinical and non-clinical parameters that may be found useful in monitoring and case management of the clients on CAB-LA PrEP. In addition, the existing National MoH PrEP Register will be revised to update the required documentation of salient data elements for clients on either oral and CAB-LA PrEP and for the purpose of data collation, aggregation, and reporting, especially where there are no SmartCare EHR entry portals. Appendix 1 shows the matrix of the ad-hoc M&E indicators required for all demonstration sites to report to National MoH and the National PrEP Task Force for the purpose of producing accountability reports to PEPFAR and other stakeholders. These indicators have been adapted from the Zambian National PrEP M&E Framework. [14]

Handling Seroconversion Data

For all clients enrolled on CAB-LA PrEP, we will document all HIV seroconversions. Any participant who HIV seroconverts while using CAB-LA PrEP will be provided with post-test HIV counseling and be initiated on ART as per national guidelines. With participant's permission, an additional blood specimen will be collected for drug resistance testing at the time of HIV diagnosis to identify the presence of HIV drug resistance mutations and provide an opportunity to adjust the ART regimen if needed. The results of the HIVDR test will be returned to the facility for communication to the client as per routine MoH procedures. [15]

Appendices

Appendix 1: Ad-hoc M&E Indicators for Tracking and Reporting

Indicators	Rationale	Data Source	Reporting Frequency
Number of oral PrEP users who are willing to transition to CAB-LA PrEP disaggregated by age category, sex, and population type	Measure CAB-LA PrEP demand rate	PrEP transition screening Form	Monthly
Number of oral PrEP users screened and eligible for transitioning to CAB-LA PrEP disaggregated by age category, sex, and population type	Measure CAB-LA PrEP transition eligibility	PrEP transition screening Form	Monthly
Percent of oral PrEP users screened and eligible for transitioning to CAB-LA PrEP disaggregated by age category, sex, and population type	Measure CAB-LA PrEP transition eligibility	Calculated from PrEP transition screening Form	Monthly
Number of CAB-LA PrEP adoptees started on month 0 course disaggregated by age category, sex, and population type (PrEP_NEW)	Measure of CAB-LA PrEP initiation	Revised PrEP Initial Form	Monthly
Number of adoptees continuing CAB-LA PrEP at month 2, 4, 6, 8, 10, 12 and 12+ course disaggregated by age category, sex, and population type (PrEP_CT)	Measure of retention on CAB-LA PrEP Mean CAB-LA PrEP retention period	Revised PrEP Follow-up Form Revised PrEP Register	Monthly and quarterly
Numbers of clients on CAB-LA PrEP reporting or screened and having adverse drug reaction or adverse drug event disaggregated by the degree of severity	Measure of toxicity of the medical product or technology	ADR Screening Form Adverse Drug or Vaccine Reaction and Event Report Forms	Monthly and quarterly
Number of clients on CAB-LA PrEP who stopped PrEP due to ADR or ADEs (PrEP_TOX)	Measure of toxicity of the medical product or technology	ADR Screening Form Adverse Drug or Vaccine Reaction and Event Report Forms	Monthly and quarterly
Number of clients on CAB-LA PrEP who stopped PrEP disaggregated by the reason(s) for stopping, and age category, sex, facility	Measure of attrition on CAB-LA PrEP	Revised PrEP Follow-up Form Revised PrEP Register	Monthly and quarterly
Number of clients on CAB-LA PrEP who were reported HIV seroconverted	Measure of CAB-LA PrEP prevention outcome	Revised PrEP Follow-up Form Revised PrEP Register	Monthly and quarterly
Number of clients on CAB-LA PrEP reported HIV seroconverted with blood sample taken for HIV drug resistance testing	Measure of CAB-LA PrEP prevention outcome	HIV Drug Resistance Laboratory Request Form Revised PrEP Register	Monthly and quarterly
Number of clients on CAB-LA PrEP reported HIV seroconverted showing HIV drug resistance	Measure of CAB-LA PrEP HIVDR	HIV Drug Resistance Laboratory Request Form DISA Database at National Level	Monthly and quarterly
Number of clients on CAB-LA PrEP reported HIV seroconverted showing HIV drug resistance	Measure of CAB-LA PrEP HIV DR	Calculated from the DISA dataset at National Level	Monthly and quarterly

Appendix 2: Timelines for Introduction of CAB-LA PrEP

Task	2023									2024		
	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar
Policy Environment												
Development of CAB-LA PrEP Implementation Plan	X	X	X	X								
Submission of plan to Ministry of Health approval				X								
Registration of CAB-LA in Zambia and application of Waiver	X	X	X	X	X	X	X					
Service Delivery												
Updating of PrEP guidelines and training package				X								
Produce and disseminate service delivery tools/job aids, SOPs & IEC materials						X	X					
Finalization of PrEP communication strategy						X						
Revising data collection tools					X							
Development of site capacity assessment tool					X							
Secure supplies for CAB-LA PrEP service delivery					X	X	X	X	X	X	X	X

Continuation of Table 8

Task	2023									2024		
	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar
Human Resources												
Training of healthcare providers (clinical, nursing, laboratory, pharmacy)						X	X	X				
Training of demand generation teams							X	X	X	X		
HIVDR Monitoring												
HIVDR protocol finalization and submission to IBR					X	X						
HIVDR capacity assessment and capacity enhancement plan developed					X	X	X					
HIVDR training for site and laboratory staff							X	X				
HIVDR surveillance activities									X	X	X	X

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