MATRIX-007

Safety Evaluation following Exposure to Cabotegravir-, Dapivirine- and Tenofovir-based PrEP during Pregnancy (CARE PrEP)

MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women

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A Non-IND study

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MATRIX
Advancing R&D of Innovative
HIV Prevention Products for Women

MATRIX-007

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LIST OF ABBREVIATIONS AND ACRONYMS

AGYW	Adolescent girls and young women
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ANC	Antenatal care
APR	Antiviral Pregnancy Registry
ART	Antiretroviral therapy
ARV	Antiretroviral
CAB	Community advisory board
CAB-LA	Long-acting injectable cabotegravir
CATALYST	Catalyzing access to new prevention products to stop HIV
CDC	Centers for Disease Control and Prevention (US)
CFR	Code of Federal Regulations
CRF	Case report form
CRM	Clinical research manager
DAIDS	Division of AIDS
DM	Data management
DRA	Drug regulatory authority
DSMB	Data and Safety Monitoring Board
DTG	Dolutegravir
DVR	Dapivirine vaginal ring
EMA	European Medicines Agency
EPDS	Edinburgh Postnatal Depression Scale
FHI 360	Organization formerly known as Family Health International
FTC	Emtricitabine
GBD App	Global Birth Defects Application for Description and Coding of Birth Defects
GCP	Good Clinical Practice
GDP	Good Documentation Practices
HHRC	Harare Health and Research Consortium
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH E6	International Conference for Harmonization Guideline for Good Clinical Practice
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LMP	Last menstrual period
LTFU	Loss to follow up
MATRIX	A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women
MOSAIC	Maximizing Options to Advance Informed Choice for HIV Prevention
MWRI	Magee-Womens Research Institute
OHRP	Office for Human Research Protections

PEPFAR	US President's Emergency Plan for AIDS Relief
PI	Principal Investigator
PID	Participant identifier
PPROM	Preterm premature rupture of membranes
PrEP	Pre-exposure prophylaxis
SAE	Serious adverse event
SEV	Study Exit Visit
SOP	Standard operating procedures
SSP	Study specific procedures
TDF	Tenofovir disoproxil fumarate
USAID	US Agency for International Development
Wits RHI	Wits Reproductive Health and HIV Institute
WHO	World Health Organization

MATRIX-007

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MATRIX-007

Safety Evaluation following Exposure to Cabotegravir-, Dapivirine- and Tenofovir-based PrEP during Pregnancy (CARE PrEP)

INVESTIGATOR SIGNATURE FORM

Version 1.0; July 3, 2024

MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women

Funded by:
US Agency for International Development (USAID)

A Non-IND study

I, the Country Principal Investigator, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); USAID regulations (2 CFR 200 and 22 CFR 225); standards of the International Conference for Harmonization Guideline for Good Clinical Practice (ICH E6); Institutional Review Board/Independent Ethics Committee (IRB/IEC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., USAID) and institutional policies.

I agree to maintain all study records in accordance with protocol-specified protections of participants' confidentiality and with local IRB/IEC policies and procedures. Study records must be maintained on-site for the entire implementation period of the study and a minimum of at least three years after completion of research. MATRIX will inform the investigator/institution as to when these documents no longer need to be retained.

I have read and understand the information in this protocol, including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Country Principal Investigator (print)

_____ _____
Signature of Country Principal Investigator Date

MATRIX-007

Safety Evaluation following Exposure to Cabotegravir-, Dapivirine- and Tenofovir-based PrEP during Pregnancy (CARE PrEP)

PROTOCOL SUMMARY

Short Title: CARE PrEP Study

Funders: USAID

Protocol Co-Chair: Katherine Bunge, MD, MPH

Protocol Co-Chair: Njambi Njuguna, MBChB, MSc, MPH

Sample Size: MATRIX-007 will enroll up to 800 pregnant CATALYST study participants and their infants, with a minimum target of approximately 500.

Study Population: CATALYST study participants exposed to an antiretroviral (ARV)-based HIV prevention method during pregnancy and their infants.

Study Sites: Approximately three CATALYST study sites in each of the following countries:

- Kenya
- Lesotho
- Zimbabwe

Study Design: MATRIX-007 is a prospective observational cohort study of CATALYST study participants exposed to ARV-based HIV prevention methods – long-acting injectable cabotegravir (CAB-LA), dapivirine vaginal ring (DVR) or tenofovir-based oral pre-exposure prophylaxis (PrEP) – during pregnancy and their infants. Enrollment will be favored for pregnant participants exposed to CAB-LA compared to DVR or oral PrEP.

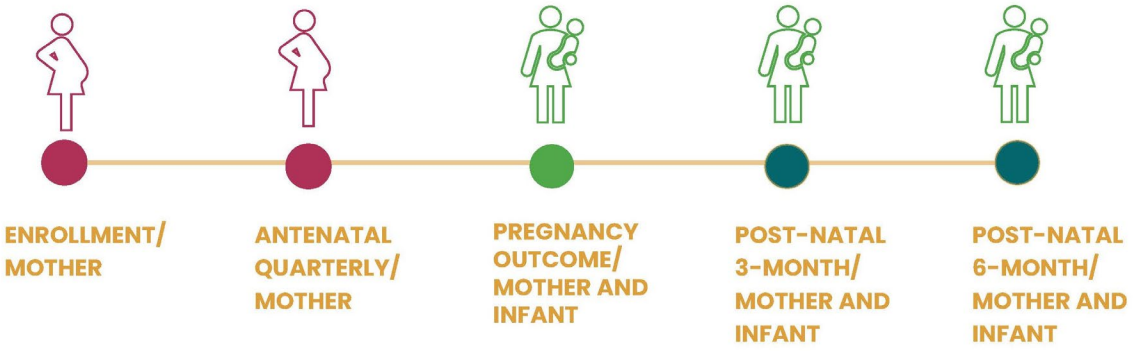
Study Duration: Up to 15 months of follow-up expected per pregnant participant (duration of pregnancy after enrollment plus 6 months post-pregnancy) and up to 6 months of follow-up expected per participant infant. The total duration of the study will be dependent upon the number of pregnancies occurring within the parent CATALYST study. Ideally, accrual will remain open until the minimum target sample size of approximately 500 pregnant participants is reached. However, accrual will be stopped early if needed to allow all participants the opportunity to complete 6 months of post-partum follow-up before the end of the Cooperative Agreement award.

Study Products: Pregnant participants will have exposure to at least one ARV-based HIV prevention method (CAB-LA, DVR, oral PrEP) as part of the CATALYST

study but MATRIX-007 will not include the administration of any study product.

Study Regimen: Pregnant participants will be followed approximately quarterly up to 6 months post-pregnancy. Participants' infants will be followed approximately quarterly up to 6 completed months of life.

Figure 1: Study Visit Schedule



Primary Objectives:

Pregnancy Outcomes

- To describe outcomes of pregnancies with exposure to one or more ARV-based HIV prevention products received in the CATALYST study.

Infant Malformations

- To describe selected infant malformations resulting from pregnancies with exposure to one or more ARV-based HIV prevention products received in the CATALYST study.

Primary Endpoints:

Pregnancy Outcomes

- Frequency of the following pregnancy outcomes:
  - Full term live birth (≥37 0/7 weeks of gestation)
  - Premature live birth (<37 0/7 weeks of gestation)
  - Pregnancy loss before 20 0/7 weeks of gestation
  - Pregnancy loss at or after 20 0/7 weeks of gestation

Infant Malformations

- Frequency of the following infant malformations:
  - Major malformations (those with surgical, medical, or cosmetic importance, ascertained up to 6 months of age)

Secondary Objectives:

Pregnancy Complications

- To describe selected complications observed during pregnancies with exposure to one or more ARV-based HIV prevention products received in the CATALYST study.

Infant Outcomes

- To describe the frequency of deaths of infants born to mothers with exposure during pregnancy to one or more ARV-based HIV prevention products received in the CATALYST study.
- To describe growth parameters of infants born to mothers with exposure during pregnancy to one or more ARV-based HIV prevention products received in the CATALYST study.

Secondary Endpoints:

Pregnancy Complications

- Frequency of the following pregnancy complications:
    - Maternal death
    - Hypertensive disorders of pregnancy
    - Chorioamnionitis
    - Puerperal sepsis
    - Endometritis
    - Antepartum hemorrhage
    - Postpartum hemorrhage
    - Preterm premature rupture of membranes (PPROM)
    - Fever of undetermined etiology

Infant Outcomes

- Frequency of infant deaths (in the first 6 months of life)
- Infant growth parameters
    - Weight at birth, three, and six months of age
    - Length at birth, three, and six months of age

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Safety Evaluation following Exposure to Cabotegravir-, Dapivirine- and Tenofovir-based PrEP during Pregnancy (CARE PrEP)
Protocol Number:	MATRIX-007
Short Title:	CARE PrEP Study
Date:	July 3, 2024

1.2 Funding Agency Identification

Funding Agency:

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2 INTRODUCTION

2.1 Background

HIV incidence remains relatively high in eastern and southern African settings, despite expansion of HIV care and treatment, and is particularly high among specific groups such as adolescent girls and young women (AGYW) and pregnant and breastfeeding populations (PBFP).[1-4] Fortunately, there are three products proven to reduce the risk of HIV acquisition: oral daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) pre-exposure prophylaxis (PrEP), a monthly dapivirine vaginal ring (DVR), and bimonthly intramuscular long-acting injectable cabotegravir (CAB-LA).

The World Health Organization (WHO) currently recommends use of TDF/FTC oral PrEP in pregnant and lactating women at risk of HIV[5], although guidelines regarding use in pregnancy and lactation differ by country. The WHO recommended the DVR as an additional prevention choice for women at substantial risk of HIV in 2021, and in 2022 recommended CAB-LA as an additional prevention choice for people at substantial risk of HIV.[6, 7] The WHO requires additional safety data on both DVR and CAB-LA use during pregnancy and breastfeeding before extending their recommendations to PBFP, although the recently completed MTN-042/DELIVER study on DVR use during pregnancy[8, 9] may provide sufficient safety data to do so for the DVR.

Maximizing Options to Advance Informed Choice for HIV Prevention (MOSAIC) is a five-year program funded by the U.S. President's Plan for AIDS Relief (PEPFAR) through the U.S. Agency for International Development (USAID) to help accelerate the introduction and scale-up of new and emerging biomedical HIV prevention products for AGYW and other women. MOSAIC activities are focused on advancing access to and uptake within a multiproduct market that includes options such as oral PrEP, the DVR (also called PrEP ring) and CAB-LA (also called CAB PrEP). MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women, is a five-year program funded by PEPFAR through USAID to expedite the research and development of HIV prevention products for women – including products designed to protect against both HIV and pregnancy – that in addition to being safe and effective, will be acceptable, affordable, scalable and deliverable in the settings where they are needed most. MATRIX activities are focused on the early research and development of HIV prevention products. Together, these two USAID programs focus on different stages of HIV prevention product research in pursuit of one common goal: expanding HIV prevention choices for all women throughout the life course.

The CATALYST study is a MOSAIC global project designed to deliver informed PrEP choice across multiple PrEP products for women in PEPFAR/USAID public health service delivery sites, building on existing PrEP service delivery within sites and in accordance with PEPFAR and national guidelines for PrEP service delivery. This mixed-methods study is being conducted in two stages to describe implementation of each new product when it becomes available (i.e., DVR in Stage I and CAB-LA in Stage II) in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe. These countries were selected based on high HIV incidence among women and current or anticipated introduction of DVR and CAB-LA PrEP, in addition to existing tenofovir-based oral PrEP delivery, thus creating feasible settings to study the delivery of informed PrEP choice. A sub-set of the CATALYST cohort

population will be participants who enroll while pregnant or become pregnant during study follow-up and are exposed to antiretroviral (ARV)-based PrEP through the study.

CATALYST participants will have access to PrEP products approved by the regulatory authority in each country. This applies to pregnant and breastfeeding participants as well. Pregnant and breastfeeding CATALYST participants will have access to tenofovir-based oral PrEP at all clinical sites; however, access to DVR and CAB-LA PrEP will vary depending on the national guidelines. As part of the CATALYST program, pregnancy outcomes will be assessed at each follow-up CATALYST visit, but these data will be based on participant report and antenatal care (ANC) card review by a data collector when available. As an implementation study, CATALYST is intended to reflect real world access. Participants are not reimbursed for their routine PrEP visits, and there are limited study related clinical procedures beyond pregnancy testing.

This cohort of pregnant CATALYST participants has the potential to provide critically important pregnancy safety data for all three PrEP modalities beyond the limited data collected in the CATALYST study; this is especially true for CAB-LA PrEP. The MATRIX-007 study is a MATRIX project designed to collect high quality pregnancy safety data from this cohort of CATALYST participants. A common criticism of pregnancy research is that gestational ages are not precise and therefore true rates of prematurity are difficult to ascertain. In MATRIX-007, ultrasounds done between 8 and 24 weeks and provided by the study will ensure accurate gestational age dating. Infant surface exams will also be conducted to ensure accurate description of infant malformations and growth parameters. In addition, travel reimbursement for participants' MATRIX-007 visit should facilitate high retention, ANC and delivery records review by a clinician will ensure accurate clinical data collection, and infant surface exams through 6 months of life will add valuable information.

2.2 Long-acting Injectable Cabotegravir

Cabotegravir extended-release suspension, a long-acting integrase inhibitor, was approved by the U.S. Food and Drug Administration (FDA) on 20 December 2021. This announcement followed the results of two randomized controlled trials for CAB-LA, both of which showed it to be highly effective in reducing the risk of HIV acquisition. CAB-LA has been approved in other countries, and approval is anticipated in the MATRIX-007 study countries by the time accrual starts.

When given according to package directions, CAB-LA may persist at detectable levels in plasma for a year or longer following discontinuation. The long elimination half-life of CAB-LA raises special considerations for pregnancies, which may be exposed to active drug long after an injection has been received. During this tail period, drug levels can persist at sub-prophylactic concentrations and this may contribute to resistance mutations, including to other HIV integrase strand transfer inhibitors like dolutegravir (DTG). The extent to which this possibility may pose a risk in the context of vertical HIV transmission is unknown.

Available data from developmental and reproductive toxicology studies, as well as limited data from pregnancies observed in clinical research contexts, do not suggest that CAB-LA exposure poses a risk for adverse outcomes during pregnancy.[10, 11] Although evidence has evolved regarding the potential association between DTG exposure in pregnancy and neural tube defects

(with recent evidence dismissing prior concerns) the shared class between cabotegravir and DTG has been cited as rationale for continued study of CAB-LA exposure in pregnancy.[10, 11]

HPTN 084 was a Phase 3 study to evaluate the safety and efficacy of CAB-LA compared to daily oral TDF/FTC when used as PrEP by HIV-uninfected, cisgender women in sub-Saharan Africa. The study enrolled 3224 participants and was designed to continue until 2022, but positive interim results led an independent Data and Safety Monitoring Board to recommend that the study sponsor stop the blinded part of the study and share the results in 2020. Both CAB-LA and oral TDF/FTC were found to be safe, well tolerated and effective, and CAB-LA was found to be superior to oral TDF/FTC in preventing HIV acquisition in women (0.2 HIV infections per 100 person years in the CAB-LA arm vs. 1.85 HIV infections per 100 person years in the oral TDF/FTC arm).[12] The HPTN 084 open label extension study began enrolling eligible HPTN 084 participants in 2022. While the open label extension of HPTN 084 will include data collection on pregnancy outcomes, a dedicated pregnancy study with linkages to the CATALYST study represents a unique opportunity to collect key outcomes outside the context of clinical research.

2.3 Dapivirine Vaginal Ring

On 23 July 23 2020, the DVR received a positive scientific opinion from the European Medicines Agency (EMA) under Article 58 for its use in HIV prevention by cisgender women ages 18 and older in low- and middle-income countries.[13] The WHO included the DVR on its prequalification list of medicines the following year and formulated a conditional recommendation that the DVR "may be offered as an additional prevention choice for women at substantial risk of HIV infection (defined as HIV incidence >3 per 100 person-years in the absence of PrEP) as part of combination prevention approaches".[14] While not approved for use in the US, the DVR has been approved for use in other countries, including those taking part in MATRIX-007.[15]

MTN-042/DELIVER is a Phase 3b study of DVR and oral TDF/FTC PrEP to assess safety, adherence, and acceptability when used during pregnancy. Participants were enrolled in three sequential cohorts, with cohort 1 enrolling pregnant participants from 36 0/7 weeks to 37 6/7 weeks gestation; cohort 2 enrolling those from 30 0/7 weeks to 35 6/7 weeks gestation and cohort 3 from 12 0/7 weeks to 29 6/7 weeks gestation. In total, 558 women and their infants were enrolled across the 3 cohorts, and infants are followed for one year after birth in all 3 cohorts. The primary study objective is to describe maternal and infant safety profiles and pregnancy outcomes among participants using study product during pregnancy. Primary endpoints for the study are composite maternal safety, composite infant safety, and pregnancy outcomes. Composite safety for both mother and infant encompasses all serious adverse events (SAEs) and grade 3 or higher adverse events (AEs) as per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Pregnancy outcomes are classified as either full term live birth (≥37 weeks), preterm live birth (<37 weeks), or intrauterine fetal demise ≥20 weeks. Secondary endpoints for the study include adherence, acceptability, infant drug levels and pregnancy complications. Regarding pregnancy complications, each participant is assessed for hypertensive disorders of pregnancy, chorioamnionitis, puerperal sepsis and endometritis, preterm premature rupture of membranes (PPROM), hemorrhage, and fever of unclear etiology.

The study has completed enrollment and all maternal participants have been exited. Infant follow up will be complete in May 2024. There have been no safety concerns identified in either arm and rates of preterm delivery and pregnancy complication were similar between the oral PrEP

arm, the DVR PrEP arm, and local background rates.[8, 9] Similarly, no safety signals were observed among participants of the Phase 3 trials (MTN-020/ASPIRE and IPM 027/The Ring Study) and open label extension trials (MTN-025/HOPE and IPM 032/DREAM) who became pregnant during the study and were exposed to the DVR during early pregnancy.[16-18] Results from the MTN-042 study, in combination with MTN-016 data from the DVR Phase 3 and open label extension trial participants, provide a strong body of evidence to indicate the DVR is well tolerated when used during pregnancy.

2.4 Tenofovir-based Oral Pre-exposure Prophylaxis

Tenofovir-based oral PrEP was first approved by the US FDA in 2012 as once-daily Truvada (200 mg FTC/300 mg TDF), in combination with safer sex practices, to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.[19] Truvada for oral PrEP has since been approved for use by adults at high risk of sexually acquiring HIV-1 infection in other countries, including those taking part in MATRIX-007.[15]

Results from the Antiretroviral Pregnancy Registry (APR) Interim Report, 1January1989 through 31July2017, showed exposures for pregnant women to FTC- and TDF-containing regimens in the first trimester were associated with birth defect rates of 2.3% (60 of 2614 live births for FTC regimens; 76 of 3342 live births for TDF regimens). Compared to the background birth defect rate of 2.7% for pregnant women in the U.S. (reference population), there was no association between FTC or TDF exposure and overall birth defects.[20] A recent systematic review noted multiple research gaps, including limited data on uncommon perinatal outcomes (e.g., congenital anomalies) and outcomes in HIV-uninfected women who use PrEP during pregnancy and/or lactation. However, the authors concluded that early safety studies of PrEP among pregnant women without HIV infection are reassuring and ongoing/planned studies will contribute extensive new data to bolster the safety profile of PrEP use in pregnancy.[21]

Because oral tenofovir has been used for the treatment of HIV and hepatitis during pregnancy there is sufficient safety data for the WHO to recommend its use during pregnancy.[5] It is being included in this observational study to provide an informal comparison group in the analysis.

2.5 Rationale for Study Design

MATRIX-007 is an observational cohort study of CATALYST participants exposed to ARV-based HIV prevention methods during pregnancy and their infants. The underlying objective of the study is to estimate negative health outcomes of mothers and infants exposed to CAB-LA, DVR and oral PrEP. There is a considerable body of safety data available on DVR and oral PrEP use during pregnancy, and said data indicates both methods are well tolerated to use during pregnancy. However, less is known about CAB-LA use during pregnancy. MATRIX-007 enrollment will thus be favored for pregnant participants exposed to CAB-LA to help address this knowledge gap.

MATRIX-007 is not designed to determine whether a strong, physiological causal relationship exists between drug exposure levels and negative pregnancy outcomes. However, MATRIX-007 results, particularly when combined with data from other observational studies, will allow practitioners, regulators and policymakers to make better informed inferences about potential risks to maternal and infant health from exposure to PrEP during pregnancy, and thus better informed recommendations about PrEP use during pregnancy. While we do not expect the results

of this study on their own to inform expansion of product use during pregnancy, these results are expected to be reviewed in the context of a broader set of findings from a range of studies collecting safety outcomes following CAB-LA exposure during pregnancy.

3 OBJECTIVES

3.1 Primary Objectives

Pregnancy Outcomes

- To describe outcomes of pregnancies with exposure to one or more ARV-based HIV prevention products received in the CATALYST study.

Infant Malformations

- To describe selected infant malformations resulting from pregnancies with exposure to one or more ARV-based HIV prevention products received in the CATALYST study.

3.2 Secondary Objectives

Pregnancy Complications

- To describe selected complications observed during pregnancies with exposure to one or more ARV-based HIV prevention products received in the CATALYST study.

Infant Outcomes

- To describe the frequency of deaths of infants born to mothers with exposure during pregnancy to one or more ARV-based HIV prevention products received in the CATALYST study.
- To describe growth parameters of infants born to mothers with exposure during pregnancy to one or more ARV-based HIV prevention products received in the CATALYST study.

4 STUDY DESIGN

4.1 Identification of Study Design

MATRIX-007 is a prospective observational cohort study of CATALYST study participants exposed to ARV-based HIV prevention methods – CAB-LA, DVR or tenofovir-based oral PrEP – during pregnancy and their infants. Enrollment will be favored for pregnant participants exposed to CAB-LA compared to DVR or oral PrEP.

4.2 Summary of Major Endpoints

Primary Endpoints:

Pregnancy Outcomes

- Frequency of the following pregnancy outcomes:
  - Full term live birth (≥37 0/7 weeks of gestation)
  - Premature live birth (<37 0/7 weeks of gestation)
  - Pregnancy loss before 20 0/7 weeks of gestation
  - Pregnancy loss at or after 20 0/7 weeks of gestation

Infant Malformations

- Frequency of the following infant malformations:
  - Major malformations (those with surgical, medical, or cosmetic importance, ascertained up to 6 months of age)

Secondary Endpoints:

Pregnancy Complications

- Frequency of the following pregnancy complications:
  - Maternal death
  - Hypertensive disorders of pregnancy
  - Chorioamnionitis
  - Puerperal sepsis
  - Endometritis
  - Antepartum hemorrhage
  - Postpartum hemorrhage
  - PPROM
  - Fever of undetermined etiology

Infant Outcomes

- Frequency of infant deaths (in the first 6 months of life)
- Infant growth parameters
  - Weight at birth, three, and six months of age
  - Length at birth, three, and six months of age

4.3 Description of Study Population

The study population will consist of CATALYST study participants exposed to an ARV-based HIV prevention method during pregnancy that meet the criteria outlined in Sections 5.2 and 5.3, and their infants.

4.4 Time to Complete Accrual

The time to complete accrual at each study country will be dependent upon the number of pregnancies occurring within the parent CATALYST study. Ideally, accrual will remain open until the minimum target sample size of approximately 500 pregnant participants is reached; however,

accrual may be stopped early to allow all participants the opportunity to complete 6 months of post-partum follow-up before the end of the Cooperative Agreement award.

4.5 Study Groups

MATRIX-007 will enroll up to 800 pregnant participants across the CATALYST study sites, with a minimum target of approximately 500, favored to CAB-LA exposure compared to DVR or oral PrEP exposure. MATRIX-007 will also enroll all infants born to the pregnant participants. See Section 10.3 for more details.

4.6 Expected Duration of Participation

Once enrolled in MATRIX-007, participant mothers are expected to complete up to 15 months of follow-up (duration of pregnancy after enrollment plus 6 months post-pregnancy) and their infants are expected to complete up to 6 months of follow-up. The total duration of the study will be dependent upon the number of pregnancies occurring within the parent CATALYST study. Ideally, accrual will remain open until the minimum target sample size of approximately 500 participant mothers is reached, and the study will continue until all enrolled participants have completed study participation. However, accrual may be stopped early to allow all participants the opportunity to complete 6 months of post-partum follow-up before the end of the Cooperative Agreement award.

4.7 Sites

MATRIX-007 sites will be located within or near the health facilities delivering PrEP services that are CATALYST study sites. Approximately three CATALYST study sites in the following countries will take part in MATRIX-007, selected based on pregnancy incidence and volume and integration of maternal and child health services:

- Kenya
- Lesotho
- Zimbabwe

5 STUDY POPULATION

5.1 Selection of the Study Population

The study population will consist of participants who enroll while pregnant or who become pregnant during the CATALYST study. Participants must still be pregnant and may participate in MATRIX-007 without participation of their infants. However, infants whose mothers have not enrolled in MATRIX-007 will not participate.

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be used to ensure the appropriate selection of pregnant study participants.

5.1.1 Recruitment

Potential participants will be recruited for MATRIX-007 as soon as possible after identification of pregnancy. The CATALYST study team will identify participants who enroll while pregnant or who become pregnant during participation in the parent CATALYST study and refer them for MATRIX-007. See Section 7.1 for additional pre-screening details.

Participants can be enrolled for subsequent pregnancies. Informed consent will be sought from participants for all subsequent pregnancies. Please see MATRIX-007 Study Specific Procedures (SSP) Manual for additional details.

5.1.2 Retention

Once a participant is enrolled in MATRIX-007, the study team will make every effort to retain the participant in follow-up to minimize possible bias associated with loss-to-follow-up (LTFU). An average retention rate of 95% will be targeted across study countries. Country Principal Investigators (PIs)/designees will develop and implement local standard operating procedures (SOP) to target and ensure high rates of retention.

5.2 Inclusion Criteria

Potential participants must meet all the following criteria prior to Enrollment:

1) At time of Enrollment, aged 18 years (inclusive) or older or emancipated minor as defined by the potential study participant's country, verified per local SOP.

2) Able and willing to:
    - Provide written informed consent for mother and infant to be screened for and enrolled in MATRIX-007 in one of the study languages (as specified in local SOP).
    - Provide adequate locator information, as defined in local SOPs.
    - Comply with all study requirements and procedures.
    - Receive antenatal care, by participant report.
    - Provide permission to contact participant's antenatal, intrapartum, postpartum and pediatric care provider(s) and to obtain copies of antenatal, intrapartum, postpartum and pediatric care records.
    - Provide permission to access the participant's CATALYST study data.

3) Estimated to be less than 34 weeks gestation (≤33 weeks and 6 days) at time of Enrollment per the MATRIX-007 SSP Manual.

4) HIV-uninfected based on testing performed at Enrollment (per national HIV testing algorithm in each study country).

    Note: HIV rapid testing may be omitted if HIV testing occurred as part of PrEP or ANC visit within 5 days of Enrollment and MATRIX-007 study staff can verify the test results or if participant has initiated antiretroviral therapy (ART) and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual.

5) Current or past participant in the CATALYST study.

6) Currently pregnant, as evidenced by HCG positive urine result at Enrollment.

Note: Pregnancy testing may be omitted if pregnancy testing or ultrasound confirming pregnancy occurred as part of PrEP or ANC visit within 5 days of Enrollment and MATRIX-007 study staff can verify the test results as outlined in the MATRIX-007 SSP Manual.

7) Current pregnancy exposed to ARV-based prevention method received during the CATALYST study per participant report, with exposure defined as follows:
    - Received at least one dose of CAB-LA PrEP within 180 days of estimated date of conception, as determined by local SOP.
    - Used DVR PrEP at least 21 days out of the last month (i.e., 28 days).
    - Used tenofovir-based oral PrEP at least 21 days out of the last month (i.e., 28 days).

5.3 Exclusion Criteria

Potential participants must not meet any of the following criteria:

1) Per participant report at Enrollment, intends to do any of the following during the scheduled period of study participation:
    - Relocate away from any of the study-linked CATALYST sites.
    - Travel away from any of the study-linked CATALYST sites for three or more months.

2) Positive HIV test at Enrollment.

    Note: HIV rapid testing may be omitted if HIV testing occurred as part of PrEP or ANC visit within 5 days of Enrollment and MATRIX-007 study staff can verify the test results or if participant has initiated ART and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual.

3) For CATALYST study participants exposed only to DVR and/or oral PrEP, estimated date of conception less than a month (i.e., 28 days) prior to enrollment.

4) Has any condition that, in the opinion of the Country PI/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

5.4 Infant Enrollment

Infants are prospectively selected for inclusion in MATRIX-007 when their mothers enroll in the study, and enter the study when they are born. If an infant is deemed too ill to undergo specific study procedures as outlined in Sections 7.4-7.6, the Country PI/designee may opt to omit those procedures. Participants will be asked to complete six months of follow-up for their infants but can decline further participation at any time.

5.5 Co-enrollment Guidelines

Co-enrollment in other studies is permitted by this protocol.

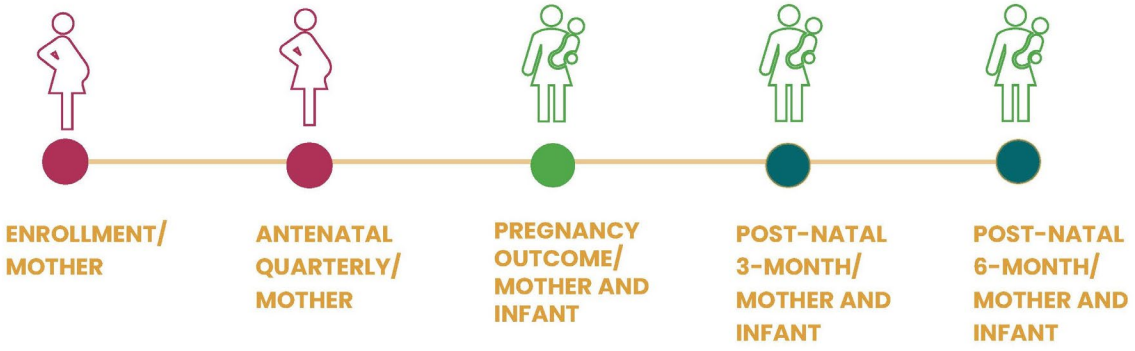
6 STUDY PRODUCT

MATRIX-007 will not include the administration of any study product.

7 STUDY PROCEDURES

An overview of the study visits and evaluations schedule is provided in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across study countries as well as to specify the visit windows are provided in the MATRIX-007 SSP Manual. All study visits will be separate from CATALYST study visits but can be scheduled to coincide with CATALYST visits when feasible and convenient. Visits other than the Enrollment Visit may be conducted at the participant's home or at another location if the participant is unable to have the visit on-site and they provide consent for off-site visits.

Figure 2: Study Visit Schedule



7.1 Pre-screening Procedures

CATALYST study staff will identify CATALYST participants who are pregnant and exposed to PrEP and inform them about MATRIX-007. If interested in participating in MATRIX-007, CATALYST study staff will ask participants to provide permission to share contact information with MATRIX-007 study staff or to be provided the information to contact MATRIX-007 staff directly.

MATRIX-007 study staff will consult with their local Institutional Review Boards/Independent Ethics Committees (IRB/IEC) regarding pre-screening potential pregnant CATALYST participants. De-identified information recorded for pre-screening purposes will be stored at the MATRIX-007 study site in compliance with local IRB/IEC requirements.

MATRIX-007 study staff will contact potential participants to explain the study and ascertain elements of presumptive eligibility, to be confirmed at enrollment visits. Presumptively eligible participants will be scheduled for an enrollment visit. Any potential participant who at any time expresses an interest in involving their current sexual partner and/or family members in

discussions about study participation will be encouraged to bring them to the study site, where a staff member can explain the study and answer any questions they may have.

7.2 Enrollment Visit

Screening and enrollment will ideally take place on the same day, but may be split if needed (e.g., records not on hand, participant has yet to meet inclusion criteria for exposure to DVR or oral PrEP). Potential participants will be instructed to bring antenatal records (e.g., ANC card) with them to the Enrollment Visit, if they have them. If required per local laws and regulations, a signed record release form will be obtained. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined. Participants who meet eligibility criteria and consent to participate in the study will be referred for an obstetric ultrasound to confirm gestational age, if adequate results are not available. Ideally, the ultrasound will take place between 8 and 24 weeks estimated gestation and before the first antenatal quarterly visit. Please see MATRIX-007 SSP Manual for additional details, including obstetric ultrasound parameters.

Note: Potential participants who fail their first screening attempt may be re-screened once.

Table 1: Enrollment Visit

Enrollment Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent for screening and enrollment • Obtain signed medical records release and ANC provider information (if required per local laws/regulations) • Assign a unique participant identifier (PID) • Collect/update/review contact/locator information • Assess/confirm eligibility • Provide reimbursement • Schedule obstetric ultrasound for gestational age confirmation, if adequate records not available • Schedule next visit, if applicable
Counseling		• HIV pre- and post-test counseling[2]
Clinical		• Collect demographic information • Collect/update/review maternal medical history[1] • Collect/update/review maternal pregnancy history • Blood pressure, height and weight • Detection of fetal heart tones via Doppler (if gestational age estimated at >16 weeks) • Review applicable test results/exam findings
Point of Care Tests	**Blood**	• HIV rapid test(s)[2] • Syphilis rapid test(s)[3]
	Urine	• Urine pregnancy test[4]

[1] To include medication review, including PrEP use when applicable

[2] HIV rapid testing will be done per local standard of testing; participants with a positive rapid HIV test will be referred back to the CATALYST study site or public sector clinic for confirmatory testing per the national testing algorithm in each study country; HIV rapid testing and pre- and post-test counseling may be omitted from this study visit if HIV testing occurred as part of PrEP or ANC visit within 5 days of the

study visit and MATRIX-007 study staff can verify the test results or if participant has initiated ART and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual
[3] Syphilis rapid testing will be done per local standard of testing; participants with a positive rapid syphilis test will be referred outside the MATRIX-007 study site for additional testing if needed and for treatment per local standard of care; syphilis testing may be omitted from this study visit if MATRIX-007 study staff can verify a documented negative result performed with a MATRIX-approved test during pregnancy and in the prior 3 months, as outlined in the MATRIX-007 SSP Manual
[4] Pregnancy testing will be done per local standard of testing; pregnancy testing may be omitted from study visits if pregnancy testing or ultrasound confirming pregnancy occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results as outlined in the MATRIX-007 SSP Manual

7.3 Antenatal Quarterly Visits

Quarterly visits will occur approximately every 12 weeks from the time of enrollment until the pregnancy outcome occurs. If the pregnancy outcome occurs before a scheduled quarterly visit, the visit should be omitted and replaced with the pregnancy outcome visit.

Table 2: Antenatal Quarterly Visits

Antenatal Quarterly Visits		
Component		**Procedures**
Administrative and Regulatory		• Collect/update/review contact/locator information • Provide reimbursement • Schedule next visit
Counseling		• HIV pre- and post-test counseling[2]
Clinical		• Collect/update/review maternal medical history[1] • Collect/update/review maternal pregnancy history • Review available obstetric ultrasound results • Review/confirm gestational age • Blood pressure and weight • Detection of fetal heart tones via Doppler (if gestational age estimated at >16 weeks) • Review applicable test results/exam findings
Point of Care Tests	**Blood**	• HIV rapid test(s)[2] • Syphilis rapid test(s)*[3]

[1] To include medication review, including PrEP use when applicable
[2] HIV rapid testing will be done per local standard of testing; participants with a positive rapid HIV test will be referred back to the CATALYST study site or public sector clinic for confirmatory testing per the national testing algorithm in each study country; HIV rapid testing and pre- and post-test counseling may be omitted from this study visit if HIV testing occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results or if participant has initiated ART and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual
[3] Syphilis rapid testing will be done per local standard of testing; participants with a positive rapid syphilis test will be referred outside the MATRIX-007 study site for additional testing if needed and for treatment per local standard of care; syphilis testing may be omitted from this study visit if MATRIX-007 study staff can verify a documented negative result performed with a MATRIX-approved test during pregnancy and in the prior 3 months, as outlined in the MATRIX-007 SSP Manual

7.4 Pregnancy Outcome Visit

All participants will have a follow-up visit as soon after their pregnancy outcome as possible, and optimally within 5 days. If the outcome resulted in a live birth, the infant(s) should ideally be present for the visit with the participant. As permitted by local regulations, participants who complete this visit within 5 days may be provided additional reimbursement to compensate for the additional inconvenience, and participants may be provided with a baby care package (e.g., diapers, blanket, etc.) or other small token to further encourage retention. If the Pregnancy Outcome Visit is missed, a subset of these procedures will be made up as part of an interim visit or completed as part of the next scheduled visit as outlined in the MATRIX-007 SSP Manual.

Table 3: Pregnancy Outcome Visit

Pregnancy Outcome Visit		
Component		**Procedures**
Administrative and Regulatory		• Assign a unique PID for infant[5] • Collect/update/review contact/locator information • Provide reimbursement • Schedule next visit[5]
Counseling		• HIV pre- and post-test counseling[2]
Clinical		• Collect/update/review maternal medical history[1] • Collect/update/review maternal pregnancy history • Ascertain pregnancy outcome • Maternal depression screening • Maternal blood pressure* • Review applicable test results/exam findings • Collect/update/review infant medical history[5] • Infant physical exam – weight, length, surface exam[5] • Infant feeding assessment[5]
Point of Care Tests	**Blood**	• Maternal HIV rapid test(s)[2] • Maternal syphilis rapid test(s)*[3]

* If indicated

[1] To include medication review, including PrEP use when applicable

[2] HIV rapid testing will be done per local standard of testing; participants with a positive rapid HIV test will be referred back to the CATALYST study site or public sector clinic for confirmatory testing per the national testing algorithm in each study country; HIV rapid testing and pre- and post-test counseling may be omitted from this study visit if HIV testing occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results or if participant has initiated ART and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual

[3] Syphilis rapid testing will be done per local standard of testing; participants with a positive rapid syphilis test will be referred outside the MATRIX-007 study site for additional testing if needed and for treatment per local standard of care; syphilis testing may be omitted from this study visit if MATRIX-007 study staff can verify a documented negative result performed with a MATRIX-approved test during pregnancy and in the prior 3 months, as outlined in the MATRIX-007 SSP Manual

[5] Omit in cases of pregnancy loss; Omit assigning infant PID, scheduling next visit and infant physical exam in cases of infant loss

7.5 Post-natal Month 3 Visit

All participants who deliver live births will bring themselves and their infant(s) for a follow-up visit 3 months and 6 months following delivery.

Table 4: Post-natal Month 3 Visit

Post-natal Month 3 Visit		
Component		**Procedures**
Administrative and Regulatory		• Collect/update/review contact/locator information • Provide reimbursement • Schedule next visit[5]
Counseling		• HIV pre- and post-test counseling[2]
Clinical		• Collect/update/review maternal medical history[1] • Maternal depression screening • Maternal blood pressure* • Review applicable test results/exam findings • Collect/update/review infant medical history • Infant physical exam – weight, length, surface exam[5] • Infant feeding assessment
Point of Care Tests	**Blood**	• Maternal HIV rapid test(s)[2] • Maternal syphilis rapid test(s)*[3]
	Urine	• Urine pregnancy test*[4]

* If indicated

[1] To include medication review, including PrEP use when applicable

[2] HIV rapid testing will be done per local standard of testing; participants with a positive rapid HIV test will be referred back to the CATALYST study site or public sector clinic for confirmatory testing per the national testing algorithm in each study country; HIV rapid testing and pre- and post-test counseling may be omitted from this study visit if HIV testing occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results or if participant has initiated ART and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual

[3] Syphilis rapid testing will be done per local standard of testing; participants with a positive rapid syphilis test will be referred outside the MATRIX-007 study site for additional testing if needed and for treatment per local standard of care; syphilis testing may be omitted from this study visit if MATRIX-007 study staff can verify a documented negative result performed with a MATRIX-approved test during pregnancy and in the prior 3 months, as outlined in the MATRIX-007 SSP Manual

[4] Pregnancy testing will be done per local standard of testing; pregnancy testing may be omitted from study visits if pregnancy testing or ultrasound confirming pregnancy occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results as outlined in the MATRIX-007 SSP Manual

[5] Omit in cases of infant loss

7.6 Post-natal Month 6 Visit / Study Exit Visit (SEV)

This visit constitutes the Study Exit Visit (SEV). If post-pregnancy, this set of visit procedures will also be performed as the Early SEV for infants and participants who are withdrawn from the study for any reason, if they are willing to bring themselves and/or their infants in for a final study visit.

Table 5: Post-natal Month 6 Visit / SEV

Post-natal Month 6 Visit / SEV		
Component		**Procedures**
Administrative and Regulatory		• Provide reimbursement
Counseling		• HIV pre- and post-test counseling[2]
Clinical		• Collect/update/review maternal medical history[1] • Maternal depression screening* • Maternal blood pressure* • Review applicable test results/exam findings • Collect/update/review infant medical history • Infant physical exam – weight, length, surface exam[5] • Infant feeding assessment
Point of Care Tests	**Blood**	• Maternal HIV rapid test(s)[2] • Maternal syphilis rapid test(s)*[3]
	Urine	• Urine pregnancy test*[4]

* If indicated

[1] To include medication review, including PrEP use when applicable

[2] HIV rapid testing will be done per local standard of testing; participants with a positive rapid HIV test will be referred back to the CATALYST study site or public sector clinic for confirmatory testing per the national testing algorithm in each study country; HIV rapid testing and pre- and post-test counseling may be omitted from this study visit if HIV testing occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results or if participant has initiated ART and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual

[3] Syphilis rapid testing will be done per local standard of testing; participants with a positive rapid syphilis test will be referred outside the MATRIX-007 study site for additional testing if needed and for treatment per local standard of care; syphilis testing may be omitted from this study visit if MATRIX-007 study staff can verify a documented negative result performed with a MATRIX-approved test during pregnancy and in the prior 3 months, as outlined in the MATRIX-007 SSP Manual

[4] Pregnancy testing will be done per local standard of testing; pregnancy testing may be omitted from study visits if pregnancy testing or ultrasound confirming pregnancy occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results as outlined in the MATRIX-007 SSP Manual

[5] Omit in cases of infant loss

7.7 Follow-up Procedures for Participants Who Become Infected with HIV, Who Become Pregnant, Who Experience a Pregnancy Loss, Who Experience an Infant Loss, or Who Experience a Maternal Death

7.7.1 Participants Who Become Infected with HIV

If a participant tests positive for HIV after the Enrollment Visit, the participant will be referred back to the CATALYST study site or to a public health sector clinic for confirmatory testing per the national testing algorithm in each study country and for referral for treatment. The participant will continue study follow-up, if willing. Please reference the MATRIX-007 SSP Manual for additional details.

7.7.2 Participants Who Become Pregnant

If a participant becomes pregnant after the Pregnancy Outcome Visit, the participant will be referred to local health care services. The participant may be offered re-enrollment in MATRIX-007, if willing. Informed consent will be sought from participants for all subsequent pregnancies. Please reference the MATRIX-007 SSP Manual for additional details.

7.7.3 Participants Who Experience a Pregnancy Loss

Participants will receive fetal heart monitoring at all antenatal visits including Enrollment if gestation is estimated at >16 weeks. Participants will be immediately referred to antenatal care if suspected pregnancy loss or other clinically significant adverse finding is detected. If a participant experiences a pregnancy loss during the study, the participant will be encouraged to complete a final study visit. All study procedures for the Pregnancy Outcome Visit will be performed with the exception of infant-related procedures (i.e., infant medical history, infant physical exam, and infant feeding assessment) and the participant will be offered appropriate mental health referral services as needed. If the participant is willing, additional follow-up may be conducted as needed (e.g., due to incomplete data collection). Once pregnancy outcome data collection is complete, the participant can be exited from the study. Please reference the MATRIX-007 SSP Manual for additional details.

7.7.4 Participants Who Experience an Infant Loss

If a participant experiences the loss of an infant participant during the study, the participant will be encouraged to complete the next visit for which they are scheduled (i.e., Pregnancy Outcome Visit or Post-natal Quarterly Visit) as their final visit. All study procedures for that visit will be performed with the exception of the infant physical exam; applicable infant-related procedures such as infant medical history and infant feeding assessment will be performed if the participant agrees. If participant is willing, additional follow-up may be conducted as needed (e.g., due to incomplete data collection). At this point the participant will be exited from the study and offered appropriate mental health referral services as needed. Please reference the MATRIX-007 SSP Manual for additional details.

7.7.5 Participants Who Experience a Maternal Death

Should the study team learn of a participant's death, they will attempt to capture the pregnancy outcome through medical records review. Infant follow-up may be continued if a legal guardian is willing, able, and consents to bring the infant(s) in for the remainder of the study visits. Otherwise, the infant(s) will be exited from the study. Please reference the MATRIX-007 SSP Manual for additional details.

7.8 Interim Visits/Contacts

Interim visits/contacts (i.e., between regularly scheduled MATRIX-007 study visits) may be performed as needed (e.g., participant reports a pregnancy complication) at any time during the study, and any visit procedures may be conducted as indicated. All interim contacts and visits will be documented in participants' study records. If a participant misses a visit, the participant may be asked to complete an interim visit to make up certain missed visit procedures, or these may

be completed by phone or at the next scheduled visit. Refer to the MATRIX-007 SSP Manual for additional details.

7.9 Counseling

HIV testing and risk reduction counseling will be provided to all participants at visits when they are tested for HIV. Participants will be monitored for symptoms of depression using the Edinburgh Postnatal Depression Scale (EPDS) – a validated depression scale designed for use with pregnant and postpartum women – which will be administered in the Pregnancy Outcome and Post-natal Quarterly Visits. Participants will be referred to counseling and/or mental health services if clinically indicated.

7.10 Clinical Evaluations and Procedures

Infant Physical Examination

Infant exam to include weight, length, and surface exam for possible congenital anomalies per the WHO guidance for newborn examination (available at https://cdn.who.int/media/docs/default-source/mca-documents/nbh/enc-course/modules/8-examination-of-the-newborn.pptx). Study staff will use the Global Birth Defects (GBD) Application for Description and Coding of Birth Defects, a validated tool to facilitate the systematic evaluation of congenital anomalies in low resource settings[22], as an aid during the infant surface exam. If permitted by the infant's mother/guardian, photos and/or videos of suspected congenital anomalies may be taken and uploaded to the GBD App to assist in clinical evaluation of the condition by a panel of experts associated with the study.

Calculation of Gestational Age

The best obstetric estimate should be used as the measure for gestational age, rather than estimates based on the last menstrual period (LMP) alone. While gestational age eligibility will be determined at enrollment based on LMP or ANC documentation of expected due date, ultrasound measurement of the fetus will be conducted between the Enrollment Visit and the first Antenatal Quarterly Visit to confirm gestational age of participants' unborn babies.

Detection of Fetal Heart Tones

Study staff will auscultate the fetal heart rate through the maternal abdomen using the handheld doppler device while the participant mother is in a comfortable position. Auscultation should occur in the absence of a uterine contraction, when the fetus is not moving. At the same time, the mother's radial pulse should be palpated to ensure that the fetal heart rate is auscultated, not the mother's.

7.11 Specimen Evaluations

Point of Care Tests

- Blood
  - HIV rapid test(s)
  - Syphilis rapid test(s)
- Urine
  - Urine pregnancy test

Point of care test results will be provided to the participant. Specimens obtained from participants will be discarded following testing and will not be stored or used for any other purposes.

7.12 Specimen Collection and Management Oversight

All study-indicated specimen testing will be completed via point of care tests (i.e., HIV and syphilis rapid tests and urine pregnancy tests) per local standard of testing. Study staff will adhere to any laboratory specifications in the MATRIX-007 SSP Manual and local SOPs for proper collection and testing of specimens. In cases where point of care test results are not available due to administrative or test error, or are invalid or not interpretable and the Country PI/designee determines reasonable to repeat, study staff are permitted to collect specimens again.

7.13 Biohazard Containment

As the acquisition of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate infection prevention control precautions will be employed by all personnel in the drawing of blood and handling of all specimens for this study as recommended by the WHO, Centers for Disease Control and Prevention (CDC) and other applicable national regulatory authorities. Waste segregation and disposal will be practiced in accordance with the biosafety guidelines at each study site.

8 ASSESSMENT OF SAFETY

MATRIX-007 is an observational study involving no investigational products or procedures associated with significant risk to participants. Therefore, few safety concerns are expected as a result of study participation.

8.1 Safety Monitoring

The safety of participants in this study is of utmost importance. Serious adverse events (SAEs), per ICH E2 definition, and social harms that are related or possibly related to study participation; other unexpected/unanticipated problems; safeguarding incidents; and protocol deviations will be documented and reported to the study team and according to IRB/IEC requirements and pre-established procedures as required by 45 CFR 46 and will be included in reports to the applicable national drug regulatory authorities (DRA) in accordance with DRA requirements.

Country PIs/designees will have written procedures for ensuring prompt reporting to the IRBs/IECs of any unanticipated problem involving risks to subjects or others. The study team will monitor for and track unanticipated problems related to study procedures and/or to participation in the study, until participants' study exit. Study staff will provide clinically appropriate treatment and/or referrals should any such problems occur.

A subgroup of the Protocol Team including the Protocol Chairs, Clinical Research Managers (CRM) and other technical area experts will be established as the Safety Sub-committee. The Safety Sub-committee will review primary and secondary endpoints and advise the study teams on study eligibility and any potential safety concerns, including SAEs and social harms, as well as any

clinical queries regarding participants. The Safety Sub-committee will meet quarterly (or more frequently if needed) and correspond through email.

8.2 Social Harms Reporting

Although study staff will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms will be reported to the Safety Sub-committee and responsible local IRB/IEC according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed.

9 CLINICAL MANAGEMENT

9.1 Clinical Findings Identified During Follow-up

Upon enrolling in the study, all participants will receive referrals for prenatal care if they have not yet started care. Any participant whose unborn baby is noted to have abnormal or clinically suspicious findings on fetal heart monitoring will be referred to local providers of antenatal care. Any infant noted to have abnormal or clinically suspicious findings on physical exam, growth monitoring and/or testing will be referred to local providers of pediatric care. In the case of identified structural anomalies and/or potential deviations from normal health, the Country PI/designee will make every effort to communicate directly with the referral entity, provided that consent has been obtained for this purpose.

9.2 HIV Infection

HIV testing will be performed at designated study visits per the local standard of testing. Potential participants who test positive for HIV prior to enrollment will not be enrolled in the study but will be referred back to the CATALYST study site or to a public health sector clinic for confirmatory testing per the national testing algorithm in each study country. Enrolled participants who test positive for HIV will be referred back to the CATALYST study site or to a public health sector clinic for confirmatory testing and referral for treatment as needed. They will continue their follow-up visits, if willing. Study staff will not be responsible for paying for HIV-related care.

9.3 Syphilis Infection

Syphilis testing will be performed at designated study visits per the local standard of testing. Potential participants who test positive for syphilis prior to enrollment will not be prohibited from enrolling in the study and will be referred outside the MATRIX-007 study site for additional testing if needed and for treatment per the local standard of care. Enrolled participants who test positive for syphilis will be referred outside the MATRIX-007 study site for additional testing if needed and

for treatment per the local standard of care. They will continue their follow-up visits, if willing. Study staff will not be responsible for paying for syphilis-related care.

9.4 Pregnancy

Pregnancy testing will be performed at the enrollment visit as part of eligibility determination. Pregnancy testing may be performed after pregnancy outcome as indicated. Pregnancy testing may be omitted from study visits if pregnancy testing or ultrasound confirming pregnancy occurred as part of PrEP or ANC visit within 5 days of the study visit and results can be verified by study staff. A participant who becomes pregnant after their Pregnancy Outcome Visit may be offered re-enrollment in MATRIX-007, if willing and if the study is still open to enrollment. The Country PI/designee also will refer the participant to all applicable services; however, study staff will not be responsible for paying for pregnancy-related care.

9.5 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw themselves and/or their infants from the study for any reason at any time. Country PIs/designees also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Country PIs/designees must notify the Safety Sub-committee immediately of any such instances. Participants also may be withdrawn if USAID, MATRIX, MOSAIC, government or regulatory authorities, including the Office for Human Research Protections (OHRP), or local IRB/IEC/DRA terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume study procedures and follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

MATRIX-007 is a prospective observational cohort study of CATALYST study participants exposed to CAB-LA, DVR or tenofovir-based oral PrEP during pregnancy and their infants. Enrollment will be favored for pregnant participants exposed to CAB-LA compared to DVR or oral PrEP.

10.2 Study Endpoints

Primary endpoints

Pregnancy Outcomes

- Frequency of the following pregnancy outcomes:
  - Full term live birth (≥37 0/7 weeks of gestation)
  - Premature live birth (<37 0/7 weeks of gestation)
  - Pregnancy loss before 20 0/7 weeks of gestation
  - Pregnancy loss at or after 20 0/7 weeks of gestation

Infant Malformations

- Frequency of the following infant malformations:
    - Major malformations (those with surgical, medical, or cosmetic importance, ascertained up to 6 months of age)

Secondary endpoints

Pregnancy Complications

- Frequency of the following pregnancy complications:
    - Maternal death
    - Hypertensive disorders of pregnancy
    - Chorioamnionitis
    - Puerperal sepsis
    - Endometritis
    - Antepartum hemorrhage
    - Postpartum hemorrhage
    - PPROM
    - Fever of undetermined etiology

Infant Outcomes

- Frequency of infant deaths (in the first 6 months of life)
- Infant growth parameters
    - Weight at birth, three, and six months of age
    - Length at birth, three, and six months of age

10.3 Sample Size and Power Calculations

Up to 800 pregnant participants exposed to CAB-LA, DVR, and oral PrEP are expected to be enrolled into the study, with a minimum target of approximately 500. Consequently, up to 800 infants born to the pregnant participants are also expected to be enrolled. The sample sizes are based on available resources and eligible participants recruited from CATALYST. Enrollment will favor CAB-LA users, ideally with a 3:1 ratio, but will ultimately be dependent on ARV prevalence among eligible participants. The outcomes of interest pertain to maternal and infant morbidity and mortality related to pregnancy and childbirth. These outcomes are rare as reported by the World Health Organization and meta-analyses with maximum rate estimates of 4,000 per 100,000 pregnancies and births in sub-Saharan Africa, or a rate of 4%. The underlying objective of the study is to estimate negative health outcomes of mothers and infants exposed specifically to CAB-LA. Both oral PrEP and DVR have generous evidence showing that they carry no more risk to mothers and infants than normal pregnancy and childbirth; they serve as valuable comparators. We do not expect this study to have sufficient power to detect meaningful estimates for outcome rates and differences between ARV groups. However, we provide below in Figure 3 and Table 6 power estimates for various outcome rates and differences in outcome proportions to demonstrate what would otherwise be needed or plausible considering the confines of the study. We also present in Figure 4 and Table 7 precision measurements for outcomes observed over the course of the study. These calculations are only illustrative as the data for this study will only be analyzed descriptively.

Figure 3: Graphical representation of the study's power to detect differences in outcomes between ARV groups for sample sizes n1=160 and n2=480

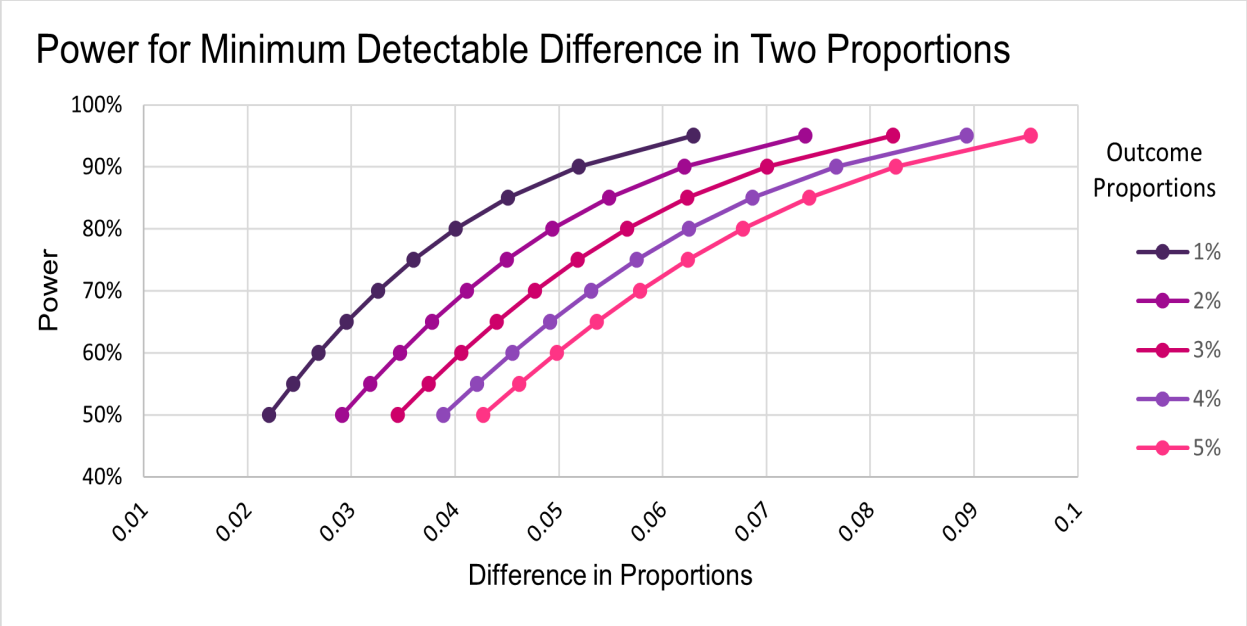


Table 6. Required minimum detectable difference in study outcomes between ARV groups needed to achieve 80% power

Minimum Detectable Difference (MDD) for 80% Power					
MDD (percentage points)	4.01%	4.94%	5.66%	6.26%	6.77%
Proportion of outcome in n1*	1.00%	2.00%	3.00%	4.00%	5.00%
Proportion of outcome in n2*	5.01%	6.94%	8.66%	10.26%	11.77%
*n1 = 160, n2 = 480, alpha = 0.05, beta = 0.80					

Figure 4: Graphical representation of point estimates for sample sizes n=160 and n=480 for study outcomes

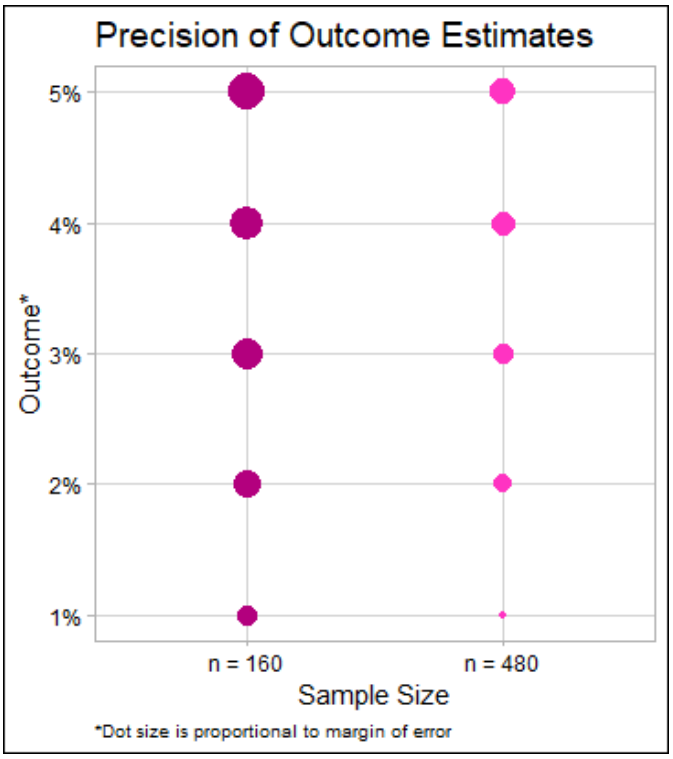


Table 7. Margin of error for foreseeable proportions in study outcomes

Outcome Proportion Estimate	Margin of Error	
	n = 160	n = 480
5.00%	±3.4%	±1.9%
4.00%	±3.0%	±1.8%
3.00%	±2.6%	±1.5%
2.00%	±2.2%	±1.3%
1.00%	±1.5%	±1.0%

10.4 Participant Accrual, Follow-up and Retention

MATRIX-007 will enroll up to 800 pregnant participants across the CATALYST study sites, with a minimum target of approximately 500, favored to CAB-LA exposure compared to DVR or oral PrEP exposure. MATRIX-007 will also enroll all infants born to the participants.

Once enrolled in MATRIX-007, participants are expected to complete up to 15 months of follow-up and their infants are expected to complete up to 6 months of follow-up. Infants from multiple-birth pregnancies are eligible for enrollment. Participants and their infants can be enrolled for subsequent pregnancies into MATRIX-007.

Once a participant has enrolled in the study, the Country PIs/designees will make every reasonable effort to retain them for the entire study period. A maximum of 5% loss-to-follow-up of enrolled pregnant women and infants will be targeted across study countries.

10.5 Data and Safety Monitoring and Analysis

10.5.1 Study Monitoring

No DSMB oversight is planned for this study. The MATRIX Clinical Trials Hub will routinely review study progress, including rates of participant accrual, retention, completion of visit procedures, and other issues. Additional reviews may take place as needed. Safety monitoring and review of primary and secondary endpoints will be done by the Safety Sub-committee.

10.5.2 Primary and Secondary Analyses

The objectives of this study are descriptive. Tables showing descriptive statistics and frequencies will be generated to present participants' demographic, clinical, and outcome data.

10.5.3 Missing Data

When feasible and necessary to complete data collection in cases of loss-to-follow-up, and with prior consent of the participant, the study team will attempt to collect this information directly from the participant's health record documentation or from facilities through chart/register abstraction and/or by contacting care providers. Source(s) of outcome data will be documented. Considering that the analytic objectives of this study are to be descriptive and to contribute to a larger body of data, missing data will clearly and appropriately be coded as such after going through data quality assurance and quality control processes at both the site and aggregate level. Imputation, substitution, or deletion methods will be considered as needed, or for larger analyses to be done with a larger body of data.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Data collection

Data collection tools will be developed by the FHI 360 Data Management team in conjunction with the protocol team. As part of the study activation process, each study site must identify source documents for all primary data collected, which may include documentation of clinical procedures, surveys with participants, infant photos/videos for review of congenital anomalies, and abstraction from available HIV and pregnancy test results and medical records of the participants (e.g., antenatal, intrapartum, postpartum and pediatric care records). Study data is entered into electronic forms using a tablet or laptop in the MATRIX-007 REDCap study database, a data management system maintained by the FHI 360 Data Management Team. Select participant data from the CATALYST study, such as demographic information, PrEP use history,

and other variables relevant to MATRIX-007 study operations and analysis will also be obtained according to an established data sharing agreement with CATALYST and with participant consent.

Each study participant will be assigned a unique study ID number that will be associated with all their study records. This study ID will be different than the study ID used for the participant in CATALYST.

Data Storage and Access

Study data will be securely stored in an access restricted server managed by FHI 360. Data will be uploaded to the server daily by site study staff. Backup copies will be created weekly by downloading the data from the server and storing it in access restricted FHI 360 SharePoint folder.

For photos/videos uploaded to the GBD Application, only pseudonymized data will be collected, i.e., using a study unique identification code for the individual rather than any personal identification details. Images are stored in a secure, private database hosted by the GBD Application. Images will be deleted off devices (phones/tablets) immediately after uploading to the GBD Application.

In accordance with the USAID Automated Directives System (ADS) 579, after acceptance of any knowledge product presenting study findings and after being cleaned of any information that could be used to personally identify participants, the quantitative survey datasets and their relevant documentation will be made available publicly in an open data repository, to the extent permissible by each country's data privacy regulations.

Data Verification and Cleaning

Data verification and cleaning will be managed by the FHI 360 Data Management Team. Data queries that will be sent to the site study staff for resolution on a weekly basis. A back up of the cleaned data will be store on the study SharePoint site hosted by FHI 360.

Study Data Retention

Upon study completion, data will be cleared from all data collection devices, such as tablets, and all stored materials will be destroyed at the sites after permission has been received from the investigators. Final datasets will be kept in password-protected electronic project files at FHI 360 for three years, per FHI 360 policy. Hard copies of relevant documents, such as signed consent forms, compensation logs, or participant logs will be kept in a locked filing cabinet at the in-country project partner's office in accordance with the project partner's retention policies. Access will be restricted to approved study staff only.

11.2 Quality Control and Quality Assurance

Country PIs/designees will conduct quality control and quality assurance procedures in accordance with relevant local IRB/IEC/DRA requirements and their institution's internal policies and procedures.

12 STUDY MONITORING

MATRIX-007 is an observational study involving no investigational products or procedures associated with significant risk to participants. As such, no external study monitoring is planned for this study. Participant safety will be routinely monitored by the Safety Sub-committee (see Section 8.1 for details). Key study metrics (e.g., accrual and retention rates, data quality, protocol deviations) will be routinely monitored by the study management team.

The study management team will do the following:

- Review informed consent forms, procedures, and documentation.
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including US Code of Federal Regulations (CFR) Title 45 Part 46 and Title 2 Parts 200 and 225.
- Perform source document verification to ensure the accuracy and completeness of study data.
- Assess implementation and documentation of internal quality management procedures.

Monitoring activities may be conducted on-site or remotely, which may include remote source document verification using methods specified for this purpose. Monitoring activities may be performed remotely in place of or in addition to on-site visits to ensure the safety of study participants and data integrity.

For on-site visits, the Country PI/designee will allow study management team members to inspect study facilities and documentation (e.g., informed consent forms, clinic records, other source documents, CRFs), as well as observe the performance of study procedures. The Country PI/designee also will allow inspection of all study-related documentation by authorized representatives of MATRIX, MOSAIC, USAID, OHRP, IRB/IEC and other local, US, or international regulatory authorities. A site visit log will be maintained at the study facility to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

Study investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, Country PIs/designees will have obtained IRB/IEC approval. Country PIs/designees will permit audits by USAID, OHRP, MATRIX, IRB/IEC, and other local, US, or international regulatory authorities or any of their appointed agents.

Changes to this protocol may be implemented by investigators prior to IRB/IEC approval, if those changes are required to eliminate apparent immediate hazards to the study participant; see 45 CFR 46.108(a)(3)(iii) under the 2018 Requirements (https://www.ecfr.gov). These changes must be documented as Protocol Deviations and reported to the Protocol Team and IRB/IEC as soon as possible; see ICH E6(R2), Good Clinical Practice, Section 4.5.4 (https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/ich-guidance-documents). In the event of a

public health emergency, investigators should adhere to the recommendations of their local institutions, IRB/IEC and local health departments. When conflicts exist between local directives, MATRIX, Protocol Team and/or USAID policies or guidance, investigators should follow the requirement that is most protective of study participants and study staff. All applicable study team members will be required to maintain current training certification in Human Subjects Protection (HSP) and/or Good Clinical Practices (GCP) through an accepted training curriculum in accordance with MATRIX's Good Documentation Practices (GDP) Policy (available at https://www.matrix4prevention.org/resources/matrix-policies). Prior to data collection, all data collectors will receive further training on the importance of privacy and confidentiality.

13.1 Institutional Review Boards/Ethics Committees

Each participating institution will be responsible for assuring that this protocol, the associated country-specific informed consent forms (ICF), and study-related documents (such as participant education and recruitment materials) are reviewed by the IRB/IEC responsible for oversight of research conducted at their study country and applicable national DRA. Any amendments to the protocol must be approved by the responsible IRBs/IECs and (if applicable) national DRA prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs/IECs must review the study at least annually. Each Country PI/designee will make safety and progress reports to their IRB/IEC and (if applicable) to their national DRA at least annually and within 3 months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. In addition, the results of all safety reviews of the study will be provided to the IRBs/IECs and (if applicable) national DRA.

13.2 Protocol Implementation

Prior to implementation of this protocol, and any subsequent full version amendments, each Country PI/designee must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB/IEC and any other applicable regulatory entities. Upon receiving final approval, Country PIs/designees will submit copies of all relevant protocol/amendment documents (i.e., IRB/IEC approval letters with a detailed list of approved documents, approved ICF documents, etc.) to the MATRIX Clinical Trials Hub Regulatory team.

The MATRIX CRM(s) will review the submitted document packet to ensure receipt of all required protocol/amendment documents prior to study activation at the study countries. Country PIs/designees will receive a Study Activation Notification from the MATRIX CRM(s) that indicates successful completion of the protocol readiness process. A copy of the Study Activation Notification should be retained in the investigator's regulatory files.

Upon receiving final IRB/IEC and any other applicable approval(s) for an amendment, study staff in activated study countries should implement the amendment immediately but are still required to submit copies of all relevant amendment documents to the MATRIX Clinical Trials Hub Regulatory team.

13.3 Study Coordination

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair(s) and Protocol Team representatives from MATRIX and USAID. Study implementation will also be guided by a common SSP Manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection and testing; clinical assessment, management, and reporting; and other study operations. Standardized study-specific training will be provided to study staff by the MATRIX CRM(s) and other designated members of the Protocol Team. Study staff based at each study country will consist of the Country PI, a study coordinator and clinical research associates who will receive training appropriate to their study roles.

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The Safety Sub-committee will address issues related to study eligibility and clinical management and reporting as needed to assure consistent case management, documentation, and information-sharing across study countries. Rates of accrual, retention, visit procedure completion, and other operational study aspects will be monitored closely by the team as well as the MATRIX Clinical Trials Hub.

13.4 Risk Benefit Statement

13.4.1 Risks

General
HIV testing may make the participant feel anxious regardless of the test results. Counseling and testing for HIV may cause worry and discomfort by learning more about risk for those conditions. A participant may become worried, sad or depressed after finding out that they have HIV. Trained study staff will be available to help participants deal with these feelings.

Finding out their HIV status could also cause problems between participants and their partners, family, or friends. The study staff will provide counselling and referral for support and/or care where required.

Participation in clinical research includes the risk of loss of confidentiality and discomfort with the personal nature of study questions. Study staff will make every effort to protect participant privacy and confidentiality during the study visits. Visits will take place in private, however, it is possible that others may learn of an individual's study participation and, because of this, may treat them unfairly or discriminate against them.

Social Harms
Although study staff will make every effort to protect participant privacy and confidentiality, it is possible that involvement in the study could become known to others and that social harms – non-medical adverse consequences – may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities.

13.4.2 Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may contribute additional safety data on the use of approved PrEP products during pregnancy. Participants also may appreciate the opportunity to contribute to the field of HIV prevention.

Participants will receive HIV risk reduction counseling, HIV testing, fetal heart monitoring, and obstetric ultrasounds, and their infants will receive physical exams. For STIs and other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to sources of care available in their community. Some participants may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations, and referrals.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to screening and enrollment. In obtaining and documenting informed consent, the Country PI and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with MATRIX's GDP Policy (available at https://www.matrix4prevention.org/resources/matrix-policies). Participants will be provided with copies of the ICF if they are willing to receive them.

In addition to the ICF, the Protocol Team will work with study staff and community representatives to develop appropriate materials about the study and a standardized approach to the informed consent process to be implemented at study countries, which will be detailed in the MATRIX-007 SSP Manual.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of importance to this study:

- The importance of adherence to the study visit and procedures schedule.
- The potential medical risks of study participation (and what to do if such risks are experienced).
- The potential social harms associated with study participation (and what to do if such harms are experienced).
- The limited benefits of study participation.
- The distinction between research and clinical care.
- The right to withdraw from the study at any time.

13.6 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Study staff will implement confidentiality protections that reflect the local study implementation plan and the input of study

staff and community representatives to identify potential confidentiality issues and strategies to address them.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas or password protected databases with access limited to study staff. All study data collection and administrative forms will be identified by unique PID number only to maintain participant confidentiality. Personally identifiable information collected for the study includes name, age, address, phone number, and health information. This information will be stored physically at the study site. All physical records that contain personal identifiers or link participants' ID numbers to identifying information, such as locator forms, permission to contact forms, ICFs, and compensation logs will be stored securely and separately from study records identified by unique PID numbers. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, including the US OHRP, USAID, and/or contractors of USAID, and other local, US, or international regulatory authorities
- MATRIX designees/representatives
- MOSAIC designees/representatives
- Study staff
- Local IRBs/IECs

13.7 Special Populations

13.7.1 Pregnant Women

Pregnant women will be offered enrollment in this study in accordance with guidelines set forth in the US 45 CFR 46.

13.7.2 Children

The CATALYST study may include participants ages 15-17. In CATALYST, only those under age 18 who met country-specific local IRB/IEC criteria for emancipated/mature minors were able to provide consent and be enrolled. MATRIX-007 study staff will reassess all participants under age 18 for emancipated/mature status per IRB/IEC policy before proceeding with study consent. Those who do not meet emancipated/mature minor criteria will not be permitted to join MATRIX-007.

Infants born to MATRIX-007 participants will be enrolled in this study in accordance with guidelines set forth in the US 45 CFR 46.

13.8 Compensation

Pending IRB/IEC approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Country-specific reimbursement amounts will be determined per local IRB/IEC/DRA guidelines and will be specified in the study ICFs of each individual study country.

If a participant becomes ill or injured as a result of participation in this study, the study staff will refer the participant for medical treatment for the injury, if needed. There is no mechanism for compensating the study participant for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the study will not be considered an injury or illness caused by study participation.

13.9 Reporting

Study staff will comply with local requirements to report cases of sexual assault or of sexual activity involving a person below the age of consent identified in the study.

13.10 Access to HIV-related Care

13.10.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV testing time point. Testing will be performed in accordance with the national testing algorithm in each study country. Counseling will be provided in accordance with standard HIV counseling policies and methods at each study country. Participants must receive their HIV test results to take part in this study.

13.10.2 Care for Participants Identified as HIV-Positive

An individual who has been identified as infected with HIV will be referred for management including prevention of vertical HIV transmission according to the local standard of care. Should a participant test positive for HIV after Enrollment Visit, follow-up procedures will be performed as per Section 7.7.1.

13.11 Study Discontinuation

This study may be discontinued at any time by USAID, MATRIX, MOSAIC, the OHRP, other local, US or international regulatory authorities, or local IRB/IEC.

14 PUBLICATION POLICY

USAID and MATRIX policies will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to USAID and MATRIX for review prior to submission.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	Antenatal		Postnatal		
	Enrollment	**Quarterly Visits**	**Pregnancy Outcome Visit**	**Month 3 Visit**	**Month 6 Visit/SEV**
ADMINISTRATIVE AND REGULATORY					
Obtain written informed consent for screening and enrollment	X				
Obtain signed medical records release and ANC provider information (if required per local laws/regulations)	X				
Assign a unique PID[5]	X		X (infant)		
Collect/update/review contact/locator information	X	X	X	X	
Assess/confirm eligibility	X				
Provide reimbursement	X	X	X	X	X
Schedule obstetric ultrasound for gestational age confirmation, if adequate records not available	X				
Schedule next visit[5]	*	X	X	X	
COUNSELING					
HIV pre- and post-test counseling[2]	X	X	X	X	X
CLINICAL					
Collect/update/review maternal medical history[1]	X	X	X	X	X
Collect/update/review maternal pregnancy history	X	X	X		
Collect demographic information	X				
Ascertain pregnancy outcome			X		
Maternal depression screening			X	X	*
Blood pressure, height, weight (height only at ENR; weight only at ENR and Antenatal Quarterly visits)	X	X	* (maternal)	* (maternal)	* (maternal)
Review applicable test results/exam findings	X	X	X	X	X
Review available obstetric ultrasound results		X			
Review/confirm gestational age		X			
Detection of fetal heart tones via Doppler (if gestational age estimated at >16 weeks)	X	X			
Infant feeding assessment[5]			X	X	X
Collect/update/review infant medical history[5]			X	X	X
Infant physical exam – weight, length, surface exam[5]			X	X	X

		Antenatal		Postnatal		
		Enrollment	**Quarterly Visits**	**Pregnancy Outcome Visit**	**Month 3 Visit**	**Month 6 Visit/SEV**
POINT OF CARE TESTS						
Blood	HIV rapid test(s)[2]	X	X	X (maternal)	X (maternal)	X (maternal)
	Syphilis test(s)[3]	X	*	* (maternal)	* (maternal)	* (maternal)
Urine	Urine pregnancy test[4]	X			*	*

X = Required
* = If indicated
[1] = To include medication review, including PrEP use when applicable
[2] = HIV rapid testing will be done per local standard of testing; participants with a positive rapid HIV test will be referred back to the CATALYST study site or public sector clinic for confirmatory testing per the national testing algorithm in each study country; HIV rapid testing and pre- and post-test counseling may be omitted from study visits if HIV or pregnancy testing occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results or if participant has initiated ART and MATRIX-007 study staff can verify the ART documentation, as outlined in the MATRIX-007 SSP Manual
[3] = Syphilis rapid testing will be done per local standard of testing; participants with a positive rapid syphilis test will be referred outside the MATRIX-007 study site for additional testing if needed and for treatment per local standard of care; syphilis testing may be omitted from this study visit if MATRIX-007 study staff can verify a documented negative result performed with a MATRIX-approved test during pregnancy and in the prior 3 months, as outlined in the MATRIX-007 SSP Manual
[4] = Pregnancy testing will be done per local standard of testing; pregnancy testing may be omitted from study visits if pregnancy testing or ultrasound confirming pregnancy occurred as part of PrEP or ANC visit within 5 days of the study visit and MATRIX-007 study staff can verify the test results as outlined in the MATRIX-007 SSP Manual
[5] = Omit at Pregnancy Outcome Visit in cases of pregnancy loss; Omit assigning infant PID, scheduling next visit and infant physical exam at Pregnancy Outcome and Post-natal Quarterly Visits in cases of infant loss

APPENDIX II: SAMPLE INFORMED CONSENT FORM – MOTHER and INFANT (Enrollment, Off-site Visit, and Photography/Video)

SAMPLE INFORMED CONSENT FORM

MATRIX-007
Safety Evaluation following Exposure to Cabotegravir-, Dapivirine- and Tenofovir-based PrEP during Pregnancy (CARE PrEP)

USAID

Version 1.0
July 3, 2024

PRINCIPAL INVESTIGATOR: *[Sites to insert]*
PHONE: *[Sites to insert]*
SHORT TITLE: CARE PrEP Study

INFORMED CONSENT
My name is _____ and I work for [INSERT NAME OF LOCAL INSTITUTION]. You are being invited to join a research study observing pregnancy outcomes for those that used "pre-exposure prophylaxis", known as PrEP, during their pregnancy. The investigator listed above is in charge of the study in this country. They are working with the Ministry of Health of [INSERT COUNTRY] and other partners to conduct this study. This study is funded by the US government's President's Plan for AIDS Relief (PEPFAR)/U.S. Agency for International Development (USAID) and conducted by MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women.

IMPORTANT THINGS YOU SHOULD KNOW
- You and your baby are being asked to take part in a research study called CARE PrEP. The purpose of this research is to learn more about the outcomes of pregnancies for CATALYST study participants who used a PrEP method provided by that study during pregnancy, and of their infants through the first 6 months of age.
- PrEP is used by people without HIV to prevent HIV. In CATALYST, you may have been offered use of oral PrEP (a daily pill), the PrEP ring (a flexible ring inserted in the vagina), and CAB PrEP (an injection given every 2 months).
- You were selected as a potential participant because the CATALYST study identified you as a participant who used one of the PrEP methods during your pregnancy, and because you are still pregnant. CARE PrEP is a separate study from CATALYST. You may be asked to provide some similar information about your pregnancy in both studies. However, we plan to collect more detailed information about your pregnancy and your baby in CARE PrEP than will be done in CATALYST.
- In this consent we also ask that you allow your baby or babies, if you deliver more than one, to participate once born. In this consent 'baby' refers to all babies born from your current pregnancy.

- This study is happening in 3 countries. We expect about 500-800 pregnant participants and their babies once born to participate in this study.
- If you are eligible and you choose for you and your baby to participate:
    - You will complete up to 7 visits, including the visit today through 6 months following your pregnancy.
    - Your baby will complete up to 3 visits between birth and about 6 months of age.
    - Study visits will take place at this location or at other locations with your permission.
    - At some visits you will be asked to complete the following: short interviews about you, your health and PrEP use, pregnancy, and health of your baby; height, weight, and blood pressure check; measure your baby's heart rate in the womb; HIV and syphilis testing; urine pregnancy testing; medical records review; ultrasound (requested 1 time); and a physical exam of your baby.
    - We will request some of your data from the CATALYST study.
- We will keep what you tell us private.
- You may also feel embarrassed to provide a urine sample or answer some sensitive questions about your health. It is also possible others may treat you unfairly if they learn of your participation in the study. Study staff will try to minimize or help address these risks.
- Taking part in this research study is voluntary. You do not have to participate, and you can stop your participation in the study at any time. Your participation in this study will not affect your participation in CATALYST.
- If you decide that you will not join this study, you can continue to access PrEP through CATALYST or through standard of care and ANC services. Study staff can provide you with additional information if you are interested.

Please take the time to read this entire form and ask questions before deciding to join the study. If you are willing for you and your baby to take part in the study, you will sign this form. A copy of this form will be offered to you. Signing this form does not mean you will be able to join the study. You must first complete the screening tests and questions to see if you are eligible. It is important to know that your and your baby's participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

WHY IS THIS RESEARCH BEING DONE?

The main purpose of this study is to better understand the outcomes of pregnancies for CATALYST study participants who used a PrEP method provided by that study during pregnancy, and of their infants through the first 6 months of age.

WHO WILL BE IN THIS RESEARCH STUDY?

CATALYST participants who are pregnant while participating in CATALYST and who used oral PrEP, PrEP ring, and/or CAB PrEP leading up to or during the pregnancy. Babies born from these pregnancies will also participate. About 500-800 pregnant people across three CATALYST study countries and their babies are expected to participate.

WHAT WILL I BE ASKED TO DO IF I JOIN THIS RESEARCH STUDY?

If willing and eligible to join, you will have up to 7 visits, including today (but not including any unscheduled visits), and your baby will have up to 3 visits.

You will come to the study facility every three months for the remainder of your pregnancy. Between now and your next visit, you may be asked to get an ultrasound scan. We will ask you to return for a visit shortly after your pregnancy ends (ideally about 5 days), and to bring your baby for this visit. Then you and your baby will return for a visit at about 3 months and 6 months after your delivery. You will be in the study for up to 15 months. You may have fewer visits depending on how far along in your pregnancy you are when you join the study and on the outcome of your pregnancy. These visits may occur at the study facility or other location such as your home or where you deliver your baby (with your permission). You will allow study staff to access your and your baby's health records and some of your CATALYST data, including basic information about yourself and your prior PrEP use.

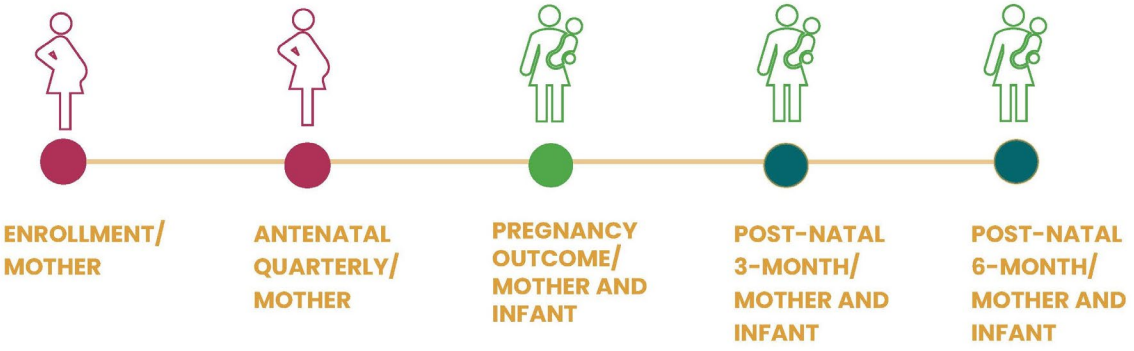
With any pregnancy, there is the possibility of losing your baby before they are born. There also is the possibility that your baby may not survive after they are born. We do not anticipate exposure during pregnancy to the PrEP products you used during CATALYST can cause these things. If either were to happen, you will be asked to complete one final visit. After that, your participation in the study would end and you would be referred to available mental health services.

DO I HAVE TO BE IN THIS STUDY?

You do not have to be in this study. If you and your baby join the study but you change your mind later about your or your baby's participation, you can inform the study staff that you no longer wish for you or your baby to participate. Your baby cannot join the study if you are not in the study. If you decide you do not want your baby to be in the study, you cannot join the study.

WHAT WILL HAPPEN DURING THE STUDY VISITS?

Your first visit will happen today after you read, discuss, understand and sign/mark this form. If eligible to join, you will be enrolled today and your baby will be enrolled once born.



The following will happen during your study visits:

- We will ask you questions about you, where you live and how to keep in touch with you, and your recent PrEP use.
- We will schedule you for an ultrasound if you have not had one or do not have complete results from your doctor with you today.
    - An ultrasound is a test that uses sound waves to check on the growth of your baby. It is done by placing a device on your belly. It does not involve any

procedures or examinations inside of you, and will not cause any harm to you or your baby.

- We will also ask you questions about other times that you were pregnant and how this pregnancy is going, including questions about your thoughts and feelings and your mood.
- Tell study staff about any health problems you might have had and medicines you take, and if anything changes between each study visit.
- Be asked permission to access your and your baby's medical records, including your delivery records to gather information about your baby at the time of birth. We may make copies of your records and store them securely. We will also ask your permission to contact your and your baby's care provider.
    - We will not tell CATALYST study staff any of your information collected as part of CARE PrEP. However, we encourage you to inform them about the outcome of your pregnancy when it happens.
- At some visits you may have a rapid HIV test, a rapid syphilis test, and/or have urine collected for a pregnancy test to confirm if you are pregnant. [SITES TO ADD COLLECTION VOLUME IF REQUIRED BY LOCAL IRB/IEC] Any blood and urine collected will be discarded after the tests are complete and will not be kept or used for any other purposes.
    - These tests may be omitted if done recently (within 5 days of visit for HIV and pregnancy testing or in your first trimester for syphilis testing) through health services such as PrEP or ANC, and these records are available to study staff for review at your visit.
- Have your height, weight, and blood pressure checked.
- At visits before your baby is born, we will monitor your baby's heartbeat with a listening device after you reach sixteen weeks of pregnancy.
    - If it sounds like something might be wrong with your baby, study staff will refer you to antenatal care for immediate follow-up.
- At visits after your baby is born, give your baby a physical exam to make sure the baby is healthy. We will measure the weight, length, and size of your baby's head, body, and limbs as part of the physical exam.
    - If it looks like something might be wrong with your baby, study staff might take pictures or video of your baby and share the pictures with experts who may be able to see what the problem might be. If you agree to have pictures/video taken of your baby, you will be asked to mark your permission at the end of this consent. We can give you a copy of any of the photographs/video. If you do not wish to have photographs/video taken of your baby, you will be able to mark at the end of this consent that no photographs/video may be taken of your baby. All picture/video taken will be securely stored with no identifiable information included.
- At visits after your baby is born, ask about your baby's feeding habits.
- We will give your and your baby referrals for other services, if you need them.

It is important for you and your baby to complete every study visit, especially the visit immediately after your baby is born. If you cannot make a scheduled visit, please tell the study staff as soon as possible so that the visit can be rescheduled. If needed, study staff may contact you by phone to complete some of the procedures listed above for you or your baby. For example, they may call you to check on your or your baby's health if you are unable to have a study visit within a week after your baby is born.

It is important that you remember that at any time during the study, study staff can answer any questions you may have about the procedures mentioned above or any other aspect of this study.

WHAT IF I BECOME INFECTED WITH HIV?
If you become infected with HIV while participating in the study, we would like you to continue to come in for your study visits. We will also provide referrals to available care and support. If you become infected with HIV, it is possible that your baby will also be at risk of becoming infected with HIV. Because of this, we may also provide referrals to have your baby tested for HIV and for available care and support.

WHAT IF I BECOME PREGNANT AGAIN?
If you become pregnant again before you exit the study, we will refer you to local health care services. You may be offered re-enrollment in MATRIX-007 if you are willing and eligible.

RISKS AND/OR DISCOMFORTS

Risks of HIV Testing
HIV testing may make you feel anxious regardless of the test results. Finding out your HIV status may cause sadness, depression, and thoughts of suicide, and may also cause problems with your family, friends, or partner.

Other Possible Risks
You may feel worried while waiting for your ultrasound results. Trained staff members are available to help you deal with any feelings or questions you have.

You may also be uncomfortable with the personal questions asked. We will make every effort to protect your privacy while you are in this study. Your visits here will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly. For example, you could have problems getting or keeping a job or being accepted by your family or community. There also is a risk to your privacy if someone else taking part in this study knows you.

BENEFITS
Participants in this study may experience no direct benefit beyond the ultrasound and infant physical exams. You or others may benefit in the future from information learned in this study. Knowledge gained from this study may provide important information to clinicians, future patients and governments about the safety of using these prevention products during pregnancy. You may also get some personal satisfaction from being part of research on preventing HIV.

This study cannot give you antenatal care or delivery services, and cannot give you or your baby general medical care. Study staff will refer you to another medical provider for care, if needed.

NEW INFORMATION
You will be told about any new information learned during this study that may affect your willingness to stay in the study. We will also tell you when study results may be available, and how to learn about them.

WHY YOU MAY BE ASKED TO LEAVE THE STUDY
You and/or your baby may need to leave the study without your permission if:

- The study is cancelled by USAID, MATRIX, the US Office for Human Research Protections (OHRP), the local government or regulatory agency, or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). An IRB/IEC is a committee that watches over the safety and rights of study participants.
- You are not able to keep appointments.
- Other reasons that may prevent you or your baby from completing the study successfully.

If you are asked to leave the study or you choose to stop participation, we will ask you to come back for one final clinic visit for you and, if applicable, your baby. Any information we collect from you and, if applicable, your baby up to that point may be kept and used for analysis. [*SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES*]

ALTERNATIVES TO BEING IN THE STUDY
[SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE: You may be able to join other studies here or in the community. There may be other places where you can go for HIV counseling and testing. We will tell you about those studies and those places if you wish.]

COSTS TO YOU
There is no cost to you for study visits, exams, or ultrasounds performed as a part of the study. This study will not provide or pay for others to provide routine prenatal care, delivery, postpartum, or routine baby care.

REIMBURSEMENT
[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT]: You will receive *[SITES TO INSERT AMOUNT* $xx*]* for your time, effort, and travel to and from the facility for each study visit. You may receive *[SITES TO INSERT AMOUNT* $xx*]* for any extra study visits.

[SITES TO INCLUDE/AMEND THE FOLLOWING PER LOCAL IRB/IEC]: You will receive an additional *[SITES TO INSERT AMOUNT* $xx*]* for completing the Pregnancy Outcome visit within 5 days of your baby being born.

CONFIDENTIALITY

- We will protect information about you and your taking part in this research to the best of our ability. We will do our best to ask any personal question in a private space where others cannot overhear you and we will not judge how you answer questions.
- Any information we collect which clearly identifies you (for example, your name, phone number, date of birth, or address) will only be shared with study staff who need it to conduct the study.
- Study staff may use your personal information, such as your name, to verify with CATALYST study staff that you participated in CATALYST and request sharing of some of your CATALYST data.
- Other information you provide that does not directly identify you will be shared with others or published. People outside of this country will have access to this information but the study will not use your name or identify you personally.

- If we learn you had a serious health-related event while participating in the study, both research staff and your provider may be informed in order to help provide you assistance and for required reporting to local regulatory and research ethics authorities.
- If we need to remind you of visits or you miss a scheduled visit, we will contact you by phone or in person based on your preference. When this contact is made you will not be identified as being in this research.

Your records may be reviewed by:
- Representatives of the US Federal Government, including USAID, MATRIX, MOSAIC, and other US, local, and international regulatory entities
- *[SITES TO INSERT APPLICABLE LOCAL AUTHORITIES]*
- Site IRB/IEC
- Study staff

The study staff will do everything they can to protect your privacy.

Other researchers conducting studies about PrEP use may want to contact you to be in their study. We will ask you if we can share your contact information with those researchers.

[SITES TO INSERT DATA PROTECTION LANGUAGE AS REQUIRED BY THEIR LOCAL IRB/IEC]

RESEARCH-RELATED INJURY
It is unlikely that you or your baby will be injured by being in this study. USAID does not have a mechanism to pay money or give other forms of financial compensation for research related injuries. You are not giving up any legal rights by signing this form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER
[*SITES TO SPECIFY INSTITUTIONAL POLICY:*] Being in this study is completely voluntary. You may choose not to join this study or for you or your baby to leave this study at any time. If you choose for you and your baby not to join or to leave the study, you can still join other studies and you can still access your current health care services. Your participation in this study will not affect your participation in CATALYST. If you want the results of the study after it is over, let the study staff members know.

PROBLEMS OR QUESTIONS
If you ever have any questions about the study, or experience any issues during the study, you should contact [*INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF*] at [*INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS*].

This research has been reviewed and approved by *[INSERT NAME(s) OF IRB/IEC]*. These committees protect your rights. If you have any questions about how you are being treated by the study or your rights as a participant you may contact them at:

[Insert IRB name(s), address(es), and contact information here]

Do you have any questions?

[SITES TO OMIT THE FOLLOWING IF NOT APPLICABLE]

CONSENT FOR OFF-SITE VISITS

Members of the research team at this site may be able to schedule off-site visits with you and your baby at your home or at another location as part of the study with your permission. For example, if you prefer not to travel to the study site before or after you deliver your baby, and you give your permission and study staff determines a visit to your home is appropriate. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the types of study procedures and the time it will take) and the procedures in-place to maintain your information in a confidential manner. However, it is important that you know that off-site visits may eventually affect your and your baby's confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

Please read carefully the following statement and initial and date one option. Choosing not to have study visit procedures outside of the study site will not affect your or your baby's participation in this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

PARTICIPANT INITIALS	
_____ Initials _____ Date	I DO agree to have study visit procedures for myself and my baby at a location other than the study site by study staff, when necessary.
_____ Initials _____ Date	I DO NOT agree to have study visit procedures for myself and my baby at a location other than the study site by study staff, when necessary.

CONSENT FOR TAKING PHOTOGRAPHS/VIDEO OF BABY

Photographs and/or videos will be taken in private, if possible. The images will be automatically deleted from the staff member's device when they are uploaded, and they will be stored on a secure and private database.

Study staff, including those outside of your country may review your baby's photographs and/or videos. It may also be necessary for a specialist to see the photographs and videos to find out more about your baby so they can understand what the problem is and maybe make suggestions for how to help. The photographs/videos and other personal information will remain private and will never be published in reports or in any form.

Please initial/mark one of the following to show whether you agree/do not agree to have photograph(s)/Video of your baby taken as may be requested by study staff:

PARTICIPANT INITIALS OR MARK	
_____ Initials/Mark Date	I DO agree to allow study staff to take photograph(s)/video of my baby
_____ Initials/Mark Date	I DO NOT agree to allow study staff to take photograph(s)/video of my baby

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/IEC:]
All of the above has been explained to me and all of my current questions have been answered to my satisfaction. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form.

☐ I agree that my and my baby's data can be shared outside of the country. I understand that my and my baby's data will be transferred to other countries that may not have the same data protection regulations as [*INSERT COUNTRY NAME*].

☐ I agree for myself and my baby to allow study staff to access our health records (e.g., PrEP, ANC, delivery, pediatric care).

☐ I agree for myself and my baby to participate as a volunteer in this study and understand that I have the right for either of us to leave the study at any time. I have been advised that this will not negatively affect my or my baby's access to health services.

I voluntarily agree for myself and my baby to be in this research study. A copy of this permission form will be given to me.

_____
Participant's Name (Print)

_____ _____
Participant's Signature Date

_____
Witness Name (Print)

_____ _____
Witness Signature Date

_____
Study Staff's Name Conducting
Consent Discussion (Print)

_____ _____
Study Staff Conducting Date
Consent Discussion (Signature)

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