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Evaluating the impact of HIV pre-exposure prophylaxis on pregnancy, infant, and maternal health outcomes in Malawi: PrIMO study protocol

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Abstract

Background Incident HIV during the perinatal period significantly impedes elimination of Mother-to-Child HIV Transmission (eMTCT) efforts. Pre-Exposure Prophylaxis (PrEP) effectively reduces HIV acquisition, and new agents like injectable Cabotegravir (CAB-LA) offer potential advantages for pregnant and breastfeeding women. The Pregnancy, Infant, and Maternal health Outcomes (PrIMO) study will compare rates of composite adverse pregnancy outcomes, and infant adverse events, growth and neurodevelopment between mother-infant dyads receiving CAB-LA and those receiving oral PrEP in Malawi.

Methods PrIMO is an observational cohort study involving: (1) the development of a PrEP Pregnancy Registry for longitudinal surveillance of pregnant women on PrEP in Malawi; and (2) the enrolment of a prospective safety cohort of 621 pregnant women initiating oral PrEP or CAB-LA and their subsequent infants. The registry will include all women continuing or initiating PrEP during pregnancy across targeted sites in Lilongwe and Blantyre districts. The safety cohort will enrol a subset of those women and their infants from Bwaila District Hospital in Lilongwe, Malawi. We hypothesize that CAB-LA's safety will be comparable to daily oral PrEP regarding adverse pregnancy outcomes, maternal/infant adverse events, and infant development. Participants in the cohort will choose either oral PrEP or CAB-LA and will be followed until 52 weeks post-delivery. Safety data will be collected from all mother-infant pairs and qualitative interviews will be conducted with a subset of purposively selected women ($n=50$) to assess the acceptability of each PrEP modality.

Discussion The PrIMO study will provide critical data on the safety of CAB-LA in pregnant and breastfeeding women and their infants. Results will guide clinical recommendations as the Malawi Ministry of Health prepares for the rollout

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of CAB-LA to this population. Evaluation of Registry implementation will inform its expansion to a nationwide safety monitoring system for PrEP use during pregnancy, with implications for similar systems in the region.

Trial Registration number NCT06158126. The study was prospectively registered (5 December 2023) in ClinicalTrials.gov.

Keywords HIV prevention, Pre-exposure prophylaxis, Cabotegravir, Birth outcomes, Infant, and maternal health outcomes

Background

The efficacy of antiretroviral therapy (ART) in impeding perinatal transmission of HIV is well established [1–7] and HIV pre-exposure prophylaxis (PrEP) antiretrovirals such as daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) effectively reduce HIV infection [8–11]. However, maternal HIV acquisition during pregnancy and breastfeeding periods remains stubbornly high [12]. Incident HIV infection during pregnancy is a significant contributor to mother-to-child HIV transmission. In Malawi, an estimated 44% of infant HIV infection in can be attributed to maternal HIV acquisition during pregnancy and breastfeeding [13]. Daily oral PrEP is safe for pregnant and breastfeeding women [10], but more studies are needed to understand the safety and acceptability of new products, such as long-acting injectable Cabotegravir (CAB-LA) among this population [14, 15].

CAB-LA provides a more discreet and less frequent dosing regimen than daily oral PrEP, and therefore could address important barriers to PrEP use among people navigating challenges related to pregnancy and early infancy [16–18]. Despite these benefits, early clinical trials on CAB-LA excluded pregnant people [17], and current studies have not yet addressed this gap [17, 19–23]. In Malawi, where the preterm birth (PTB) rate is high and a significant contributor to infant morbidity and mortality [24, 25], it is critical to understand whether and to what extent maternal exposure to newer PrEP agents may influence perinatal outcomes. Additionally, the effect of in utero or breastmilk exposure to antiretrovirals like CAB-LA on infant growth and development requires thorough longitudinal study [26, 27].

Pregnancy, Infant, and Maternal health Outcomes (PrIMO) study aims to (1) compare the safety of two PrEP modalities in pregnant women and their infants, and (2) to establish and evaluate a surveillance system for pregnant and breastfeeding women who use PrEP in Malawi. All maternal participants will have the option of oral PrEP or injectable (CAB-LA) PrEP. The study primary objective is to compare composite adverse pregnancy outcomes (including preterm birth, spontaneous miscarriage, stillbirth, and small-for-gestational-age infants) among pregnant women using CAB-LA versus oral PrEP. Secondary objectives include evaluating postpartum adverse events in mothers and infants on oral PrEP or CAB-LA, assessing growth and neurodevelopment of infants exposed to oral PrEP or CAB-LA during pregnancy and breastfeeding, determining the acceptability of oral PrEP and CAB-LA among pregnant women, and evaluating the adoption, reach, and fidelity of the nationwide surveillance system, the PrEP in Pregnancy Registry. We hypothesize that CAB-LA's safety will be comparable to daily oral PrEP regarding composite adverse pregnancy outcomes, maternal/infant adverse events, and infant growth and neurodevelopment. This study leverages our team's expertise and partnership with the Ministry of Health (MOH) in Malawi, which has prioritized pregnant women in the ongoing expanded access to CAB-LA.

Methods

Study design

PrIMO is a longitudinal observational study that will utilize mixed-methods approaches. The study will involve the establishment of a HIV PrEP Pregnancy Registry, which will include all pregnant women who are not living with HIV and are receiving PrEP at PrEP delivery sites in Malawi, and a prospective safety cohort that includes subset of women from the HIV PrEP Pregnancy Registry and their infants. All maternal participants will choose either oral PrEP (FTC/TDF or TDF/lamivudine (3TC)) or injectable PrEP (CAB-LA). Participants in the safety cohort will be categorized by their chosen PrEP modality and the timing of PrEP initiation relative to pregnancy diagnosis. We will enrol all eligible mother-infant dyads into the cohort during pregnancy, with the expectation that most will deliver at least two months after enrolment. Adherence to the World Health Organization (WHO)-adopted Malawi antenatal care (ANC) package will be ensured to optimize ANC and control for confounders [28, 29]. We will collect safety data on pregnancy, infant, and maternal health outcomes, and conduct qualitative interviews with a subset of these women to evaluate the acceptability of oral PrEP and CAB-LA. Each mother-infant dyad will be followed from enrolment throughout pregnancy and up to 52 weeks postpartum (Fig. 1). The first participant in the prospective safety cohort was enrolled on April 17, 2024.

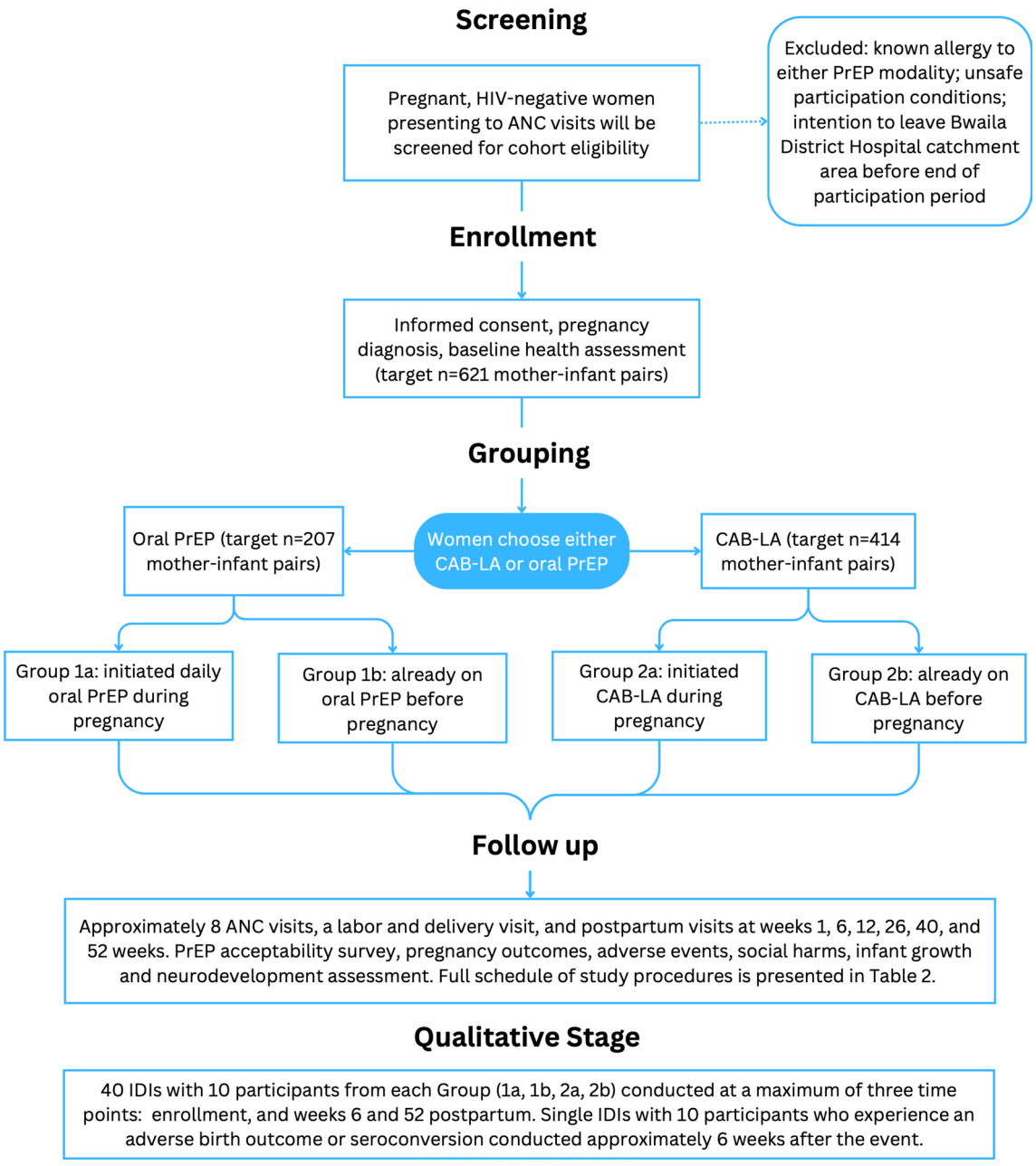

Fig. 1 Consolidated Standards of Reporting Trials flow diagram of prospective safety cohort. *Abbreviations*: ANC, Antenatal Care; PrEP, pre-exposure prophylaxis; CAB-LA, cabotegravir long-acting injectable PrEP; IDI, in-depth interview

Study sites

The PrEP Pregnancy Registry will draw from approximately 36 PrEP primary and secondary delivery sites in Lilongwe and Blantyre districts that the Malawi Ministry of Health has designated as early access sites for CAB-LA. The prospective safety cohort will include women receiving ANC at Bwaila District Hospital and planning to deliver there. Bwaila District Hospital is a public secondary level hospital with a catchment of approximately 1 million from urban and rural communities in Lilongwe and an estimated antenatal HIV prevalence of 12% [30]. It houses the busiest maternity unit in the country and provides care to approximately 150 pregnant women daily, with approximately 20,000 deliveries per year [30].

Study population

Our study safety cohort will include pregnant women who are identified as being at substantial risk for HIV and eligible for PrEP per MOH guidelines [31, 32]. All maternal participants will either be current PrEP users or those initiating PrEP at study enrolment. Additional inclusion and exclusion criteria for maternal participants are

Table 1 Inclusion and exclusion criteria for maternal participants in the prospective cohort

Inclusion criteria	Exclusion criteria
• Pregnancy confirmed by a urine pregnancy test or ultrasound • ≥ 15 years of age • Confirmed HIV-negative status • Negative for Hepatitis B surface antigen (HBsAg) • Weigh > 35 kg • Willing to provide written informed consent	• Known allergies to CAB-LA, TDF/3TC, or FTC/TDF • Significant active or chronic diseases or social circumstances that could render participation unsafe, as determined by the site investigator • Intention to leave the catchment area of Bwaila District Hospital before the scheduled end of the participation period in the study

Abbreviations: CAB-LA, cabotegravir long-acting injectable PrEP; TDF/3TC, Emtricitabine/Lamivudine; FTC/TDF, Emtricitabine/Tenofovir disoproxil fumarate

presented in **Table 1**. Infant participants will be included in the study with their mothers; no additional criteria are required for their participation. Given that the majority of new mothers in Malawi choose to breastfeed their child [33], we did not separately consider intention to breastfeed in our eligibility criteria.

Sample size calculations

The safety cohort will include an estimated 621 mother-infant pairs, with 414 pairs in the CAB-LA group and 207 pairs in the oral PrEP group. The sample size has been calculated to evaluate the non-inferiority of composite adverse pregnancy outcomes when comparing the use of CAB-LA to oral PrEP based on several assumptions. First, participants are not randomized, and we anticipate that women will choose CAB-LA over oral PrEP at a ratio of 2:1, based on observed preferences for injectable contraception over oral contraception in the catchment area. Secondly, the expected rate of composite adverse pregnancy outcomes is estimated to be 30%, with a range from 15 to 45% for both PrEP modalities [54]. Thirdly, the non-inferiority margin, which is the allowable difference in outcomes between the two groups, is set at 5%. Finally, the study is designed with an 80% power to detect this difference at a 5% significance level. Fig 2 provides further details on sample sizes for varying power levels and proportions in the treatment and control groups

Considerations for the PrEP pregnancy registry

All women enrolled in the PrEP Pregnancy Registry, regardless of their inclusion in the prospective safety cohort, will have two visits. The first visit will be at the time of pregnancy confirmation when their information is entered into the registry. At the second visit, for labour and delivery, registry administrators (RAs) will record the date of delivery and its outcome into the register, either in-person or remotely. The RAs will be community health workers (CHWs), clinicians, nurses or midwives working at the PrEP sites. Registry data collection activities will be conducted as part of routine care

Considerations for the Prospective Safety Cohort

All mother-infant dyads enrolled in the prospective safety cohort will receive five types of visits: screening, enrolment, routine ANC visits, delivery, and study-specific postpartum visits at varying intervals (**Table 2**). Interim visits will be added on an as-needed basis to repeat abnormal laboratory tests or safely monitor an adverse event. To ensure thorough monitoring and care through the study, participants will also be able to request interim visits to report adverse events or seek primary care. At each scheduled visit, the mother-infant dyad will undergo a series of clinical procedures, obstetric scans, and laboratory testing (**Table 2**). Antenatal will align with routine care and will adhere to the Malawi MOH national ANC package recommendations [28]. All clinical and laboratory adverse events will be accessed and graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events [34].

Study staff will seek informed consent from antenatal women who meet the eligibility criteria. The women will be offered a choice between injectable CAB-LA and oral PrEP (if they are not already taking it) and enrolled in the PrEP Pregnancy Registry. Mother-infant dyads will be grouped according to use of oral (FTC/TDF or TDF/3TC) versus injectable PrEP (CAB-LA), and according to PrEP use before or after pregnancy diagnosis, as follows: those who initiate daily oral PrEP (Group 1a), those who are already using daily oral PrEP (Group 1b), those who initiate injectable CAB-LA (Group 2a), and those who are already using injectable CAB-LA (Group 2b).

We will also conduct in-depth interviews (IDIs) with approximately 50 women from the prospective safety cohort to further assess acceptability of oral PrEP or CAB-LA. This subset will include 10 women each from each group (1a, 1b, 2a, and 2b (n=40)) who will be interviewed at a maximum of three time points (**Table 2**). The last 10 individuals will be purposively drawn from all groups and will include those who experience adverse obstetric outcomes (abortion, stillbirth, neonatal death, birth defects) or those who seroconvert during our study. For interviews with those who experience an adverse event, we will conduct one interview ≥ 6 weeks after the incident to allow enough time for grieving and minimise psychological distress during the interviews **(Fig. 1).**

PrEP administration

Oral PrEP (FTC/TDF or 3TC/TDF) Initiation and Counselling: Participants will receive daily oral PrEP (FTC/TDF 200 mg/300 mg, or 3TC/TDF 300 mg/300 mg one tablet daily) according to Malawi National PrEP

Table 2 Schedule of key procedures for the prospective cohort

Maternal Study Procedures	**Screening**	**Enrollment**	**4 weekly ANC visits**[5]	**L&D**	**PP 1 week**	**PP 6 weeks**	**PP 12 weeks**	**PP 26 weeks**	**PP 40 weeks**	**PP 52 weeks**
Clinical procedures										
Social and demographic information	X									
Obstetric history	X	X	X							
Pregnancy and delivery status			X	X						
PrEP Pregnancy registration[1]		X		X						
Medical & Drug history	X	X	X	X	X	X	X	X		X
Physical examination	X	X	X	X	X	X	X	X		X
Social harms questionnaire		X	X	X	X	X	X	X		X
Perceived HIV risk questionnaire			X	X	X	X	X	X		X
Intimate partner violence assessment		X	X	X	X	X	X	X		X
Social Harm Assessment		X	X	X	X	X	X	X		X
Self-reported Adherence Assessment			X	X	X	X	X	X	X	X
Client education and ANC counseling		X	X							
Study drug procedures										
PrEP prescriptions[2]		X	X	X	X	X	X	X	X	X
PrEP adherence counselling		X	X	X	X	X	X	X	X	X
PrEP acceptability surveys		X		X			X			X
Radiology										
Obstetric Ultrasound	X[3]		×[4]							
Laboratory tests										
Urine pregnancy test	X[6]									
Urine dipstick		X	X	X						
Rapid HIV antibody test	X[7]	X	X[8]	X	X	X	X	X		X
Hepatitis B Surface Antigen	X[7]									
Hemoglobin	X[7]				X					X
Complete blood count		X								
Hepatic function	X				X					X
Creatinine	X				X			X		X
Syphilis screening	X[7]									
HIV RNA (viral load)[9]			X	X	X	X	X	X		X
Storage for HIV resistance[9] testing			X	X	X	X	X	X		X
Specimen Storage										
Maternal plasma storage		X		X				X		X
Breastmilk storage				X		X		X		
Dried Blood Spot								X[10]		X[10]
Infant Study Procedures	**Screening**	**Enrollment**	**4 weekly ANC visits**[5]	**Birth Visit**	**PP 1 week**	**PP 6 weeks**	**PP 12 weeks**	**PP 26 weeks**	**PP 40 weeks**	**PP 52 weeks**
Physical examination				X	X	X	X	X	X	X
Drug history					X	X	X	X	X	X
Congenital anomalies examination				X	X	X	X	X	X	X
Nutritional assessment (including growth monitoring)					X	X	X	X	X	X
Caregiver-Reported Early Development Index (CREDI)								X	X	X
Mullen Scales of Early Learning (MSEL)								X	X	X
Laboratory tests – blood										
Infant plasma storage					X	X		X		

Table 2 (continued)

Maternal Study Procedures	Screening	Enrollment	4 weekly ANC visits[5]	L&D	PP 1 week	PP 6 weeks	PP 12 weeks	PP 26 weeks	PP 40 weeks	PP 52 weeks
Clinical procedures										
Qualitative Data Collection	**Screening**	**Enrollment**	**4 weekly ANC visits[5]**	**L&D**	**PP 1 week**	**PP 6 weeks**	**PP 12 weeks**	**PP 26 weeks**	**PP 40 weeks**	**PP 52 weeks**
First IDIs[11]		X								
Second IDIs						X				
Third IDIs										X
Adverse obstetric outcome/seroconverted			X	X	X	X	X	X	X	X

[1] All participants enrolled in the Safety Cohort will also be registered in the HIV PrEP Pregnancy Register

[2] Participants on CAB-LA get their injections every 8 weeks while those on oral PrEP will get their monthly supply at the 4 weekly visits

[3] Obstetric Ultrasound (for dating pregnancy) may be done at the time of enrolment is not done at screening

[4] Ultrasound for fetal anomaly will be conducted between 18–24 weeks of gestation only on one of the 4-weekly visits

[5] To align with the Malawi antenatal care matrix, participant will have approximately eight 4 weekly visits during pregnancy

[6] Pregnancy may be confirmed by ultrasound or pregnancy test

[7] Conduct test if the test is not available in the participant' health passports

[8] Test for HIV only when resupplying oral PrEP or CAB LA

[9] HIV RNA (viral load) and storage for HIV resistance will be done ONLY if HIV rapid test is positive

[10] For those taking oral PrEP only. DBS to be done twice only on those on oral PrEP approximately 6 and 12 months from the date of enrolment

[11] In-depth interviews (IDIs) conducted with a subset of the cohort at a maximum of 3 time points

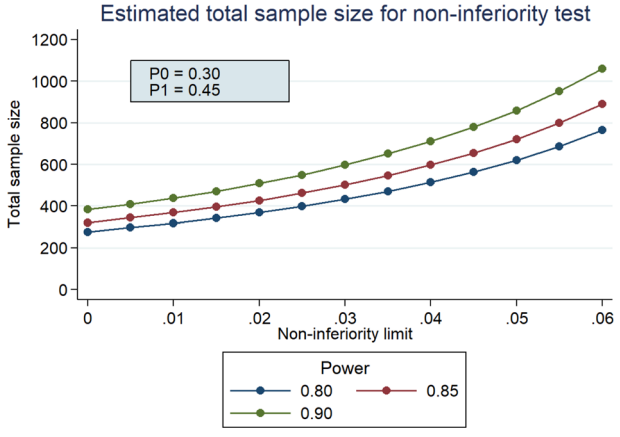

Fig. 2 Estimated total sample size for the prospective cohort

guidelines [31, 32]. Standardized counselling procedures will be utilized to inform participants about the potential side effects of oral PrEP and to clarify that oral PrEP does not prevent or treat sexually transmitted infections (STIs). Counselling on condom use will be provided according to national guidelines, and condoms will be available at the study clinic. Participants will be advised to report any side effects to the clinic for evaluation and support.

CAB LA Initiation Procedures and Counselling: The initiation of CAB-LA will align with the Malawi National PrEP guidelines [32]. This regimen involves a 600 mg intramuscular injection in the gluteal region, starting with the first dose, followed by a second dose one month later, and subsequent injections every two months. Consistent with local guidelines, there will be no oral lead-in period. Participants will receive standardized counselling about CAB-LA, including potential side effects, and clarification that CAB-LA does not prevent or treat STIs. Counselling on condom use and condom provision will be conducted as outlined above. Any side effects should be reported to the clinic for management and support.

Concomitant Medications: Within this study, 'concomitant medications' encompass any medications other than CAB-LA, FTC/TDF, or 3TC/TDF taken by maternal participants and their infants. The study will document all concomitant medications in participants' medical and medication histories during each study visit as part of the source documentation process.

Quantitative data Collection

For the prospective safety cohort, clinic staff will collect clinical and sociodemographic data through standard study case report forms and questionnaires. We will also conduct brief behavioural surveys approximately every six months during the follow-up period to investigate attitudes and beliefs about the two PrEP options as well as product-related choice and preferences. Surveys will also include a risk questionnaire regarding previous sexual activity, partners, PrEP use over the preceding six months, and self-perceived HIV risk. Risk factor assessment will draw on validated risk questionnaires such as those developed by the Partners in Prevention and

Partners PrEP study and the VOICE/HPTN 035/FEM-PrEP trials [35, 36] and HPTN 084 [17]. Some surveys will be paper-based, while others will be electronic, and both types will be administered by the research nurses.

Information for the PrEP in pregnancy registry will be collected using a paper-based registry and subsequently uploaded to an electronic registry using ScanForm technology [37], as recommended by the Malawi MOH.

Qualitative data collection

We aim to assess acceptability of oral PrEP and CAB-LA through in-depth interviews (IDIs) with a subset of women ($n=50$) purposively sampled from the safety cohort. IDIs will be conducted using a semi-structured interview guide, developed using Sekhon's theoretical framework for acceptability [38]. Sekhon's framework assesses acceptability based on anticipated or experiential cognitive and emotional responses to an intervention. It has seven constructs which are: affective attitude, burden, ethicality, intervention coherence, opportunity cost, perceived effectiveness, and self-efficacy [38]. Based on this framework, our interview guides for all women will explore HIV risk perceptions, decision making and motivation to use oral PrEP and CAB-LA, acceptability of selected PrEP regimen, perceived risks and benefits of using oral or injectable PrEP both to the mother and infant including perceived potential impact on infant birth outcomes, adherence to oral PrEP or CAB-LA, challenges to use and access, disclosure to partner and other people, and community and partner perspectives and support. For participants with an adverse obstetric outcome or who seroconverted during our study, we will explore their perspective about circumstances related to the pregnancy outcome or seroconversion, as well as perceived partner and family member perspectives about the outcome and product use during pregnancy and breastfeeding. All IDIs will be conducted in Chichewa by experienced Qualitative Research Officers fluent in both English and Chichewa. All IDIs will be audio-recorded, transcribed, and translated into English for analysis.

Recruitment and retention procedures

Recruitment for the PrEP Pregnancy Registry will be managed by RAs at various PrEP sites following national guidelines. These administrators will identify and register eligible pregnant women as part of data collection during their standard PrEP visits. Registered women will continue to receive antenatal care at their chosen clinics. Those who meet the eligibility criteria for the follow-up safety cohort will be offered participation in the cohort and enrolled by study staff. Participants in the safety cohort will receive transport reimbursement for each study visit they attend, to offset additional transport costs related to the additional study visits required beyond their routine ANC visits. The study team will track recruitment, enrolment, and retention numbers and review weekly to adjust efforts as needed.

Maternal participants will be able to withdraw themselves and their infant(s) from the study at any point. In rare cases, including if participation is deemed unsafe or if the participant moves far away from the study site, the site investigator or clinical officers may withdraw a mother-infant pair from the study. The reason for withdrawal will be recorded in study records and efforts will be made to conduct final evaluations for participants.

Clinical endpoints

For the primary objective of the safety cohort, the clinical endpoints of interest are: preterm birth (PTB), defined as delivery prior to 37 weeks of gestation; small for gestational age (SGA) infants, defined as a birth weight below the 10th percentile for their gestational age; stillbirth, defined as fetal demise at or beyond 28 weeks of gestation; and spontaneous miscarriage, which is the loss of a pregnancy before 28 weeks of gestation. Gestational age will be determined by obstetric scan using a published algorithm [39].

The clinical endpoints to evaluate infant growth include underweight, stunting, and acute malnutrition (moderate or severe) evaluated at weeks 1, 6, 12, 26, and 52. Underweight will be defined as a weight-for-age z-score (WAZ) of less than −2. Stunting will be defined by a LAZ z-score of less than −2. Malnutrition assessments will follow WHO anthropometric criteria [40]. Moderate acute malnutrition is identified by a length-for-age z-score (LAZ) between −3 and less than −2, or a Mid-Upper Arm Circumference (MUAC) between 115 millimetres and less than 125 millimetres. Severe acute malnutrition is defined by a weight-for-length z-score (WLZ) less than −3, a MUAC of less than 115 millimetres, the presence of bilateral pitting edema, or a combination of these factors [41]. Infant neurodevelopmental will be assessed using the Caregiver-Reported Early Development Index (CREDI) [42] and the Mullen Scales for Early Learning (MSEL) [43]. Assessment will be conducted at follow up visits at 6, 9, and 12 months postpartum. Neurodevelopmental delay of will be defined as low CREDI or MSEL score for age.

Safety monitoring

The research team will receive comprehensive training to assess and manage adverse events (AEs). For accurate documentation, Reportable Adverse Event forms will be used. Each AE will be assessed by a study clinician and categorized as either serious (mild, moderate, severe) or non-serious [34]. The team will follow appropriate reporting procedures for each incident. Beyond medical AEs, participants may encounter social harms

due to their involvement in the study. These instances will be documented on the Social Harm Form and will include all negative events reported by participants as a consequence of their participation, irrespective of the researcher's assessment of the impact. The study team is responsible for monitoring these issues and facilitating appropriate referrals for further support (where necessary) until they are resolved.

For grading the severity of AEs, the study will employ the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017 [44]. Additionally, congenital anomaly classification systems from the WHO will be used [45].

Data safety and monitoring

The study will develop a Data and Safety Monitoring Plan (DSMP), overseen by an external study monitoring committee. All data, both in physical and electronic formats, will be securely stored at each site. Hard copies of participant data will be stored in locked cabinets and eventually transferred to UNC Project Malawi (UNCPM) main campus in Lilongwe for secure destruction as per study site standard operating procedures. Electronic records will be kept on password-protected, encrypted devices. Qualitative interview transcripts will be anonymized, and audio recordings erased after transcription. The data access system will be tiered, with specific privileges for participants, project staff, and research investigators. Unique participant IDs will secure personal details outside the database, accessible only to authorized Research Investigators and Research Project staff.

Quality assurance will include regular data monitoring and database review, as well as site investigator supervision to ensure accurate recruitment, enrolment, and data collection. Documents will be available for IRB and OHRP (Office for Human Research Protections) inspection, maintaining compliance with research guidelines.

Confidentiality

To ensure the security of data and maintain participant confidentiality, all interviews and data collection will take place in private areas at the health facility. Any audio recordings made during qualitative interviews will be promptly transferred to a secure computer, and the original recordings will be erased. The transcripts of these recordings will not include any identifying information. Similarly, paper clinic charts and other documents will be de-identified to remove any personal details. Electronic files will be stored on encrypted devices with password protection to further ensure data security. These measures are in place to safeguard the privacy of participants and maintain integrity of the research data.

Quantitative data analysis: prospective safety cohort

For our primary objective within the safety cohort, we will utilize a composite adverse pregnancy outcome score to compare adverse pregnancy outcomes between pregnant women using CAB-LA and those using oral PrEP. This composite measure will include all occurrences of PTB, SGA, stillbirth, and spontaneous miscarriage, among by the total number enrolled in the safety cohort. We will separately assess both pregnancy outcomes and infant outcomes comparing oral PrEP and CAB-LA using logistic binomial regression models. For both models, we will estimate unadjusted and adjusted risk ratios to control for potential confounders. To compare the rate of adverse clinical or laboratory adverse events over time between women on oral PrEP and women on CAB-LA, we will use Kaplan-Meier methods. Differences in those rates will then be evaluated using a log rank test. Finally, Cox-proportional hazard models will be used to estimate the unadjusted and adjusted hazard ratios of adverse events between the oral PrEP and CAB-LA groups. We will perform similar analyses to compare rates of infant adverse clinical or adverse laboratory events between oral PrEP and CAB-LA groups.

To assess infant growth outcomes, we will first calculate the number and proportion of infants who are underweight, stunted, or acutely malnourished (with moderate acute malnutrition or severe acute malnutrition). Proportions will be calculated at the end of the study period overall and at each follow up visit. We will then compute separate logistic binomial regression models for the risk of being underweight, the risk of stunting, and the risk of varying nutritional statuses (well-nourished, moderate acute malnutrition, or severe acute malnutrition) between exposure to oral PrEP and exposure to CAB-LA.

Qualitative data analysis: prospective safety cohort

We will analyse the IDIs for the prospective safety cohort subset using content analysis on the NVivo (version 1.7) [46] data analysis platform. Content analysis will proceed via a combined deductive and inductive approach to develop a codebook using domains/constructs from Sekhon's theoretical framework for acceptability [38]. The codebook will guide the coding process for the qualitative data and the team will continue adding emerging themes during the coding process. Half of the transcripts will be double-coded and intercoder reliability will be confirmed at a level of 90% prior to proceeding. Any coding differences will be discussed and resolved. Analysed data will be displaced on matrices using Sekhon's framework to display emerging patterns [38]. Final analysis of the qualitative data will be presented in the form of summative memos.

Quantitative data analysis: the PrEP pregnancy registry

For the PrEP Pregnancy Registry, we aim to understand the implementation of the registry within routine PrEP services in Malawi. We will assess adoption, reach, and fidelity at 6, 12, and 24 months after registry implementation according to the following established definitions: [47, 48] (1) Adoption — number and percentage of targeted settings (including sites, and providers) who initiated register use by the end of the study; (2) Reach — total number of entries in the register at each site, disaggregated by observation group of interest; and (3) Fidelity — number and percent of pregnant women who had complete entries for all infant and obstetric outcomes in the register as per protocol. Study staff will collect and analyse data through registry audit at 6-, 12-, and 24-months post registry implementation.

Ethics and dissemination

The study protocol received approval from the Malawi National Health Science Research Committee (23/08/4178) and the University of North Carolina at Chapel Hill Institutional Review Board (23-2220). The study was prospectively registered in ClinicalTrials.gov; the NCT number was assigned on December 5th, 2023 (NCT06158126). Any modifications to the protocol will be submitted for approval to these committees prior to implementation changes. Dissemination of study results will occur through relevant local platforms, such as MOH technical working groups, as well as academic and public health research symposia and through peer-reviewed publications.

Discussion

The PrIMO study aims to assess the safety of CAB-LA usage compared to oral PrEP usage during pregnancy for mother-infant dyads. The PrEP Pregnancy Registry will enable longitudinal assessment of outcomes among all pregnant women under routine health care using PrEP in Malawi. The prospective Safety Cohort allows for deeper analysis of the acceptability of CAB-LA and oral PrEP and clinical safety outcomes among a subset of women and infants in the Registry. Together, these objectives align with the WHO new collaborative framework on surveillance of antiretroviral drugs in pregnancy [49] and address the need for multiple forms of safety monitoring for injectable PrEP use among pregnant individuals [14, 26]. The overarching goal of the PrIMO Study is to enable safe usage of PrEP during pregnancy through in-depth, prospective observation and longitudinal surveillance monitoring.

A significant feature of this study is that women enrolled in the safety cohort will choose between oral PrEP and injectable CAB-LA. Allowing women to choose could introduce selection bias in the construction of each group, if women who choose CAB-LA differ from those who choose oral PrEP in ways that also impact the occurrence of adverse pregnancy outcomes, or maternal and infant health outcomes. However, this design also offers a unique opportunity to closely examine real-world choices and preferences in PrEP usage while simultaneously reinforcing individual agency. Behavioural surveys and in-depth interviews will provide information to further evaluate acceptability and preferences around both PrEP modalities among pregnant women. Including oral PrEP in this study provides this opportunity for choice, and creates a control group and comparator for the group receiving CAB-LA. We acknowledge that there are often significant adherence challenges with oral PrEP [50], especially among pregnant and breastfeeding women [51], which could impact the comparability of the two modalities. To improve adherence, we will offer counselling to support women following the oral PrEP regimen and collect dried blood spots (DBS) samples to measure the concentrations of TDF in women taking oral PrEP. However, these adherence challenges will continue to be present outside of a study setting. Therefore, we posit that even if oral PrEP adherence is suboptimal, results will reflect the real-world alternative to CAB-LA.

Our study will be among the first to provide critical safety data regarding adverse pregnancy and infant outcomes up to one year post-natal among CAB-LA and oral PrEP users in a prospective cohort [52, 53]. Simultaneously, evaluation of the fidelity, reach, and adoption of a PrEP Pregnancy Registry will directly inform the implementation and scale-up of a nationwide safety surveillance system for PrEP use during pregnancy, with implications for similar systems in the region. Malawi has not yet achieved elimination of mother-to-child transmission of HIV (eMTCT) goals partly because of the incident HIV infections during pregnancy and breastfeeding [13]. PrIMO will inform optimal PrEP interventions for achieving eMTCT goals while also providing critical information on the long-term safety of the interventions for mothers and infants.

Abbreviations

AE	Adverse Event
ANC	Antenatal Care
CAB	Community Advisory Board
CAB-LA	Cabotegravir Long Acting
CHWs	Community Health Workers
CREDI	Caregiver-Reported Early Development Index
DAIDS	Division of AIDS
DBS	Dried Blood Spot
DSMP	Data Safety Monitoring Plan
eMTCT	Eliminating mother-to-child transmission of HIV
FTC/3TC	Emtricitabine
IBA	Emtricitabine/Lamivudine
FTC/TDF	Emtricitabine/Tenofovir disoproxil fumarate
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IDIs	In-depth interviews

IRB	Institutional review board
L and D	Labor and Delivery
LAZ	Length-for-age z-score
MSEL	Mullen Scales of Early Learning2
MOH	Ministry of Health
NICHD	National Institute of Child Health and Human Development
OHRP	Office for Human Research Protections
PP	Postpartum
PrEP	Pre-exposure prophylaxis
PTB	Preterm Birth
RAs	Registry Administrators
SGA	Small for gestational age
STI	Sexually Transmitted Infection
TDF/3TC	Tenofovir Disoproxil Fumarate/Lamivudine
UNCPM	University of North Carolina Project Malawi
WAZ	weight-for-age z-score
WLZ	Weight-For-Length Z-Score

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Author contributions
FS is the principal investigator and MCH is the co-principal investigator. CN is the study coordinator, GM is the medical officer, IM is the lead research nurse and FK is a project coordinator. MBC and WK are data coordinators and developed the data management components. FS, MCH, LC, TM, MBC, AB, MEH, SR and MM contributed to the study protocol development. MS and SS contributed to manuscript development. IH, RKN, VT and VM advise the study team and contribute scientific expertise. All authors have contributed to the development of this manuscript. They have read and approved the final version for publication.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol and participant consent forms were approved by the Malawi National Health Science Research Committee (23/08/4178) and the University of North Carolina at Chapel Hill Institutional Review Board (23-2220). Written or verbal informed consent will be obtained from all study participants prior to participation. Consent forms are available in Chichewa and English.

Consent for publication
Not applicable, no individual data included in this manuscript.

Competing interests
The authors declare no competing interests.

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References

1. Hoffman RM, Angelidou K (Nadia), Brummel SS, Saidi F, Violari A, Dula. Maternal health outcomes among HIV-infected breastfeeding women with high CD4 counts: results of a treatment strategy trial. HIV Clin Trials. 2018;19(6):209–24.
2. Miro JM, Manzardo C, Mussini C, Johnson M, d'Arminio Monforte A, Antinori A, et al. Survival outcomes and effect of early vs. deferred cART among HIV-Infected patients diagnosed at the time of an AIDS-Defining event: a cohort analysis. PLoS ONE. 2011;6(10):e26009.
3. Cohen Myron S, Chen Ying Q, McCauley Marybeth G, Theresa, Hosseinipour Mina C, Nagalingeswaran K, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493–505.
4. Becquet R, Bland R, Ekouevi DK, Dabis F, Newell ML. Universal antiretroviral therapy among pregnant and postpartum HIV-infected women would improve maternal health and decrease postnatal HIV transmission. AIDS. 2010;24(8):1239.
5. Twabi HS, Manda SO, Small DS. Assessing the effects of maternal HIV infection on pregnancy outcomes using cross-sectional data in Malawi. BMC Public Health. 2020;20(1):974.
6. Choudhary MC. Antiretroviral Therapy (ART) in Pregnant People With HIV Infection: Overview of HIV Antiretroviral Therapy (ART) in Pregnancy, Clinical Data on HIV Antiretroviral Therapy (ART) in Pregnancy, Factors for HIV Antiretroviral Therapy (ART) Selection in Pregnancy. MedScape [Internet]. 2022 Jun 27 [cited 2024 Apr 3]; https://emedicine.medscape.com/article/2042311-overview?form=fpf#a1
7. Goetghebuer T, Smolen KK, Adler C, Das J, McBride T, Smits G, et al. Initiation of antiretroviral therapy before pregnancy reduces the risk of infection-related hospitalization in human immunodeficiency virus–exposed uninfected infants born in a high-income country. Clin Infect Dis. 2019;68(7):1193–203.
8. Grant Robert M, Lama Javier R, Anderson Peter L, McMahan Vanessa, Liu Albert Y, Lorena V, et al. Preexposure Chemoprophylaxis for HIV Prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587–99.
9. Mofenson LM. Tenofovir pre-exposure prophylaxis for pregnant and breastfeeding women at risk of HIV infection: the time is now. PLoS Med. 2016;13(9):e1002133.
10. Joseph Davey DL, Pintye J, Baeten JM, Aldrovandi G, Baggaley R, Bekker LG, et al. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? J Int AIDS Soc. 2020;23(1):e25426.
11. Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. AIDS. 2017;31(2):213–32.
12. Graybill LA, Kasaro M, Freeborn K, Walker JS, Poole C, Powers KA, et al. Incident HIV among pregnant and breast-feeding women in sub-saharan Africa: a systematic review and meta-analysis. AIDS. 2020;34(5):761–76.

13. WHO. Key considerations for programming and prioritization. Going the 'Last Mile' to EMTCT: a road map for ending the HIV epidemic in children. In New York: UNICEF; 2020.
14. World Health Organization. Guidelines on long-acting injectable cabotegravir for HIV prevention. 2022.
15. Erlwanger A, Rocroi I, Kirtley S, Hemelaar J. Perinatal outcomes associated with pre-exposure prophylaxis for HIV prevention during pregnancy: a systematic review and meta-analysis. eClinicalMedicine [Internet]. 2024 Apr 1 [cited 2024 May 20];70. https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(24)00111-1/fulltext
16. Vickerman P, Quaife M, Kilbourne-Brook M, Mvundura M, Eakle R, Terris-Prestholt F. HIV prevention is not all about HIV – using a discrete choice experiment among women to model how the uptake and effectiveness of HIV prevention products may also rely on pregnancy and STI protection. BMC Infect Dis. 2020;20(1):704.
17. Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022;399(10337):1779–89.
18. Wara NJ, Mvududu R, Marwa MM, Gómez L, Mashele N, Orrell C, et al. Preferences and acceptability for long-acting PrEP agents among pregnant and postpartum women with experience using daily oral PrEP in South Africa and Kenya. J Int AIDS Soc. 2023;26(5):e26088.
19. PrEP Watch. Injectable CAB for PrEP [Internet]. PrEP Watch. 2023 [cited 2024 Feb 16]. https://www.prepwatch.org/products/injectable-cab-for-prep/
20. Hill LM, Saidi F, Freeborn K, Amico KR, Rosenberg NE, Maman S, et al. Tonse Pamodzi: developing a combination strategy to support adherence to antiretroviral therapy and HIV pre-exposure prophylaxis during pregnancy and breastfeeding. PLoS ONE. 2021;16(6):e0253280.
21. MTN – Microbicides Trial Network. Where we are with the DELIVER and B-PROTECTED studies [Internet]. [cited 2022 Apr 17]. https://www.mtnstopshiv.org/news/studies/mtn042
22. IMPAACT. 2026. International Maternal, Pediatric, Adolescent AIDS Clinical Trials [Internet]. [cited 2022 Jul 29]. https://www.impaactnetwork.org/studies/impaact2026
23. Njuguna I, Saidi F, Joseph Davey D, Chi BH, Pintye J, Editorial. Improving the delivery of pre-exposure prophylaxis (PrEP) to eliminate vertical HIV transmission. Frontiers in Reproductive Health [Internet]. 2024;6. https://www.frontiersin.org/articles/; https://doi.org/10.3389/frph.2024.1382548
24. World Health Organization. Malawi aims to improve quality of care for mothers and new babies [Internet]. WHO | Regional Office for Africa. 2017 [cited 2022 Apr 25]. https://www.afro.who.int/countries/malawi/news/malawi-aims-improve-quality-care-mothers-and-new-babies
25. Antony KM, Kazembe PN, Pace RM, Levison J, Phiri H, Chiudzu G, et al. Population-based estimation of the Preterm Birth Rate in Lilongwe, Malawi: making every birth count. AJP Rep. 2020;10(1):e78–86.
26. Fairlie L, Lavies D, Kalk E, Mhlongo O, Patel F, Technau KG et al. Safety surveillance for PrEP in pregnant and breastfeeding women. Frontiers in Reproductive Health [Internet]. 2023 [cited 2024 Feb 17];5. https://www.frontiersin.org/articles/; https://doi.org/10.3389/frph.2023.1221101
27. Desmonde S, Goetghebuer T, Thorne C, Leroy V. Health and survival of HIV perinatally exposed but uninfected children born to HIV-infected mothers. Curr Opin HIV AIDS. 2016;11(5):465.
28. Malawi Ministry of Health. Antenatal guidelines for Malawi. 2019.
29. World Health Organization. New guidelines on antenatal care for a positive pregnancy experience [Internet]. 2016 [cited 2022 Jul 13]. https://www.who.int/news/item/07-11-2016-new-guidelines-on-antenatal-care-for-a-positive-pregnancy-experience
30. Ministry of Health and Population, Population-Based MM, Impact Assessment HIV. 2015–2016 [Internet]. 2018 Oct. https://phia.icap.columbia.edu/wp-content/uploads/2018/10/MPHIA-SS_2018_FINAL.pdf
31. Malawi Ministry of Health. Department of HIV/AIDS. National guidelines for the provision of oral pre-exposure prophylaxis for individuals at substantial risk of HIV in Malawi. 2020.
32. Malawi, Ministry of Health. Malawi Service Delivery Guidelines and Standard Operating Procedures for the Provision of HIV Pre-Exposure Prophylaxis using Oral or Long-acting Injectable Options. 2024.
33. Chipojola R, Lee GT, Chiu HY, Chang PC, Kuo SY. Determinants of breastfeeding practices among mothers in Malawi: a population-based survey. Int Health. 2019;12(2):132–41.
34. Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. 2017.
35. Kahle EM, Huges JP, LINGAPPA JR, John-Stewart G, Celum C, Nakku-Joloba E, et al. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1 serodiscordant couples for targeted HIV-1 prevention. J Acquir Immune Defic Syndr. 2013;62(3):339–47.
36. Balkus JE, Brown E, Palanee T, Nair G, Gafoor Z, Zhang J, et al. An empiric HIV Risk Scoring Tool to Predict HIV-1 Acquisition in African Women. JAIDS J Acquir Immune Defic Syndr. 2016;72(3):333.
37. ScanForm | About [Internet]. [cited 2023 Aug 11]. https://about.scanform.qed.ai/
38. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res. 2017;17(1):88.
39. American College of Obstetricians and Gynecologists (ACOG). Methods for Estimating the Due Date [Internet]. [cited 2024 May 20]. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/05/methods-for-estimating-the-due-date
40. World Health Organization. Integrated Management of Childhood Illness [Internet]. Geneva: World Health Organization. 2014 [cited 2024 Jun 13]. 15 p. https://iris.who.int/handle/10665/104772
41. World Health Organization. Technical note: supplementary foods for the management of moderate acute malnutrition in infants and children 6–59 months of age [Internet]. [cited 2022 Jul 24]. https://apps.who.int/iris/handle/10665/75836
42. McCoy DC, Sudfeld CR, Bellinger DC, Muhihi A, Ashery G, Weary TE, et al. Development and validation of an early childhood development scale for use in low-resourced settings. Popul Health Metrics. 2017;15(1):3.
43. Carey WB, Crocker AC, Elias ER, Feldman HM, Coleman WL. Developmental-Behavioral Pediatrics [Internet]. 2009 [cited 2024 Jun 14]. 1042 p. https://shop.elsevier.com/books/developmental-behavioral-pediatrics/carey/978-1-4160-3370-7
44. DAIDS Adverse Event Grading Tables | DAIDS Regulatory Support Center (RSC). [Internet]. [cited 2024 Apr 21]. https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables
45. WHO/CDC/ICBDSR. Birth defects surveillance: a manual for programme managers. Geneva, Switzerland: World Health Organization; 2014.
46. NVivo. About NVivo [Internet]. [cited 2024 Apr 5]. https://help-nv.qsrinternational.com/20/mac/Content/about-nvivo/whats-new.htm
47. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, et al. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health. 2011;38(2):65–76.
48. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health. 1999;89(9):1322–7.
49. Renaud F, Mofenson LM, Bakker C, Dolk H, Leroy V, Namiba A, Sahin L, Shapiro R, Slogrove A, Thorne C, Vicari M, Low-Beer D, Doherty M. Surveillance of ARV safety in pregnancy and breastfeeding: towards a new framework - PubMed [Internet]. [cited 2024 Apr 21]. https://pubmed.ncbi.nlm.nih.gov/35851994/
50. Zhang J, Li C, Xu J, Hu Z, Rutstein SE, Tucker JD, et al. Discontinuation, suboptimal adherence, and re-initiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis. Lancet HIV. 2022;9(4):e254.
51. Beesham I, Dovel K, Mashele N, Bekker LG, Gorbach P, Coates TJ, et al. Barriers to oral HIV pre-exposure Prophylaxis (PrEP) adherence among pregnant and post-partum women from Cape Town, South Africa. AIDS Behav. 2022;26(9):3079.
52. Fairlie L, Lavies D, Kalk E, Mhlongo O, Patel F, Technau KG et al. Safety surveillance for PrEP in pregnant and breastfeeding women. Frontiers in Reproductive Health [Internet]. 2023 [cited 2024 Jan 29];5. https://www.frontiersin.org/articles/; https://doi.org/10.3389/frph.2023.1221101
53. Saidi F, Chi BH. Human immunodeficiency Virus Treatment and Prevention for pregnant and Postpartum women in Global Settings. Obstet Gynecol Clin North Am. 2022;49(4):693–712.
54. Herman D, Lor KY, Qadree A, Horn D, D'Souza R. Composite adverse outcomes in obstetric studies: a systematic review. BMC Pregnancy Childbirth. 2021;21:107.

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