PrIMA

PrEP IMPLEMENTATION FOR MOTHERS IN ANTENATAL CARE

PrEP Implementation for Mothers in Antenatal Care (PrIMA)

A Clinic-Level Cluster-Randomized Trial of Universal Availability Versus Targeted Offer of Oral, Daily Pre-Exposure Prophylaxis (PrEP) among Women Attending Antenatal Care Centers in Kenya

Study Protocol

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4) LIST OF ABBREVIATIONS

ANC	Antenatal care
ART	Antiretroviral treatment
ARVs	Antiretroviral drugs
AVAC	AIDS Vaccine Advocacy Coalition
CCC	Comprehensive Care Clinic
CDC	Centers for Disease Control and Prevention
CEA	Cost effectiveness analysis
Cr	Creatinine
CrCl	Creatinine clearance
DALY	Disability-adjusted life-year
DBS	Dried blood spot
DNA	Deoxyribonucleic acid
ERC	Ethics Review Committee
FGD	Focus group discussion
FTC	Emtricitabine-triphosphate
GEE	Generalized estimating equations
GoK	Government of Kenya
HBSAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HAZ	Height-for-age z-score
IDI	In-depth interview
IRB	Institutional Review Board
KEMRI	Kenya Medical Research Institute
KNH	Kenyatta National Hospital
LPV/r	Lopinavir/ritonavir
MCH	Maternal and Child Health
MOH	Ministry of Health
MSS	Mama Salama Study
MTCT	Mother-to-child transmission
NASCOP	National AIDS and STI Control Program
ODK	Open Data Kit
PMTCT	Prevention of mother-to-child transmission of HIV
PNC	Postnatal clinic
PP	Postpartum
POC	Point-of-care
PrEP	Pre-exposure antiretroviral prophylaxis
RCT	Randomized controlled trial
RNA	Ribonucleic acid
SSL	Secure Socket Layer
STI	Sexually transmitted infection
TDF	Tenofovir disoproxil fumarate
TDF/FTC	Tenofovir/emtricitabine
TDF/FTC/LPV/r	Tenofovir/emtricitabine/lopinavir/ritonavir
TFV-DP	Tenofovir-diphosphate
UNC	University of North Carolina, Chapel Hill
UON	University of Nairobi
UW	University of Washington
WHO	World Health Organization

5) FUNDING AGENCY

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6) SUMMARY

Women living in regions with high HIV prevalence are at high risk of HIV acquisition in pregnancy and postpartum because they infrequently use condoms, do not know their partner's HIV status, and have biologic changes or changes in their partner's sexual partnerships that increase susceptibility. Oral pre-exposure antiretroviral prophylaxis (PrEP) may be an attractive strategy for HIV prevention in pregnancy/postpartum; however, it is important to ensure PrEP reaches women who are at risk for acquiring HIV during pregnancy while avoiding unnecessary PrEP use during pregnancy. Clinicians and women are using PrEP in pregnancy; in qualitative studies, women, health workers and policy-makers support use of PrEP in pregnancy but advocate for models of PrEP delivery that ensure women at risk receive PrEP while minimizing unnecessary PrEP use in women not at risk. Targeting PrEP to women at greatest risk of HIV may maximize benefits, minimize potential risks, and optimize cost-effectiveness. This cluster-randomized clinical trial (RCT) in 20 Maternal Child Health (MCH) clinics in western Kenya (10 clinics per arm, at least 200 women per clinic, 4000 women overall), will compare 2 models of PrEP delivery in pregnancy. Clinics will offer universal availability of PrEP (and women self-select whether to use) or targeted offer of PrEP (i.e., offer to women identified as high risk through a standardized risk assessment and partner self-testing, and then women identified as high-risk select whether to use). Leveraging the pre-existing MCH clinic visit schedule will enable programmatically relevant assessment of PrEP uptake, use, and HIV incidence. The outcome of the study will be a model of PrEP delivery in pregnancy that optimizes effectiveness, safety, and cost-effectiveness. Our team has expertise in maternal-child HIV (John-Stewart, Kinuthia), PrEP clinical trials and implementation science (Baeten, Richardson), partner self-testing (Thirumurthy), economics and qualitative research (Barnabas, O'Malley).

AIM 1a. In a cluster-RCT, compare universal PrEP (offer to all; women self-select PrEP) to targeted PrEP (limit the offer to women identified as high risk through a standardized risk assessment and partner self-testing) for outcomes reflecting the balance of PrEP effectiveness and avoiding unnecessary PrEP exposure to women at low or no risk of HIV: HIV incidence at 9 months postpartum among all women (including those who did and did not receive PrEP) and proportion of women exposed to PrEP.
AIM 1b. To compare trial arms for proportion of women 'appropriately' on PrEP (risk factors), PrEP adherence (drug levels) and duration, partners with known HIV status, partners on ART; infant outcomes (growth, birth outcomes, HIV status).
AIM 2. To estimate the incremental cost-effectiveness of targeted PrEP compared to universal PrEP for women during pregnancy and postpartum, per HIV infection and disability-adjusted life-year (DALY) averted.
AIM 3. To qualitatively assess barriers and facilitators to uptake, adherence, acceptability, and feasibility in universal and targeted PrEP models at the organizational, provider, and individual woman level.

7) BACKGROUND

In this study we aim to compare two models of PrEP delivery in pregnant women – universal PrEP (offered to all women, women self-select) or targeted PrEP (partner HIV self-test combined with risk score to determine whether PrEP is offered). In a cluster-RCT we will compare 10 clinics randomized to universal and 10 to targeted (at least 200 women per clinic) and compare HIV incidence among all enrolled women (including those on and not on PrEP) at 9 months postpartum and the proportion of women who take PrEP. We hypothesize that PrEP can be implemented in antenatal care clinics in way that will be acceptable and used by women at risk of HIV acquisition during pregnancy. Our also hypothesize is that a targeted approach will be more specific, effective, and cost-effective – maximizing PrEP use among pregnant women at risk and minimizing PrEP use for women without risk – thus providing the best balancing of effectiveness, cost-effectiveness, and potential for unneeded medication exposure.

a) LITERATURE REVIEW

HIV Acquisition in Pregnancy and Postpartum

Women have persistent risk of acquiring HIV in pregnancy and postpartum and often do not perceive themselves to be at risk (1). In a meta- analysis of 19 studies including 22,803 person-years, HIV incidence in pregnant/postpartum women was 3.8 per 100 p-years, 4.7/100 p-years in pregnancy and 2.9/100 p-years postpartum (Figure 1) (2). These HIV incidence estimates are particularly high given that incidence estimation was among all women (not limited to those with seropositive partners) and appreciable HIV infection occurred despite decreased sexual activity in late pregnancy and early postpartum. HIV incidence estimates in pregnancy/postpartum women are as high or higher than many 'high risk' groups, such as serodiscordant couples and sex workers. Given high HIV incidence in pregnancy/postpartum, there is urgent need for effective HIV prevention in this critical period.

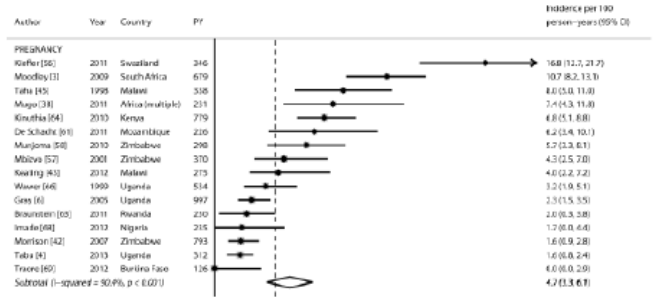


Figure 1: HIV Incidence in pregnancy (2)

Pregnancy and the postpartum period are characterized by dramatic hormonal and immunologic changes, changes in genital mucosa, and epithelial disruption during delivery

with decreased mucosal integrity postpartum (3-6). At the same time, sexual practices change markedly in this period. Sexual activity declines late in pregnancy and early postpartum, and male partners may seek other partners, and bring HIV back to the relationship (7-9). HIV acquisition in pregnancy/postpartum most often occurs among women who are unaware of their partner's HIV status. In Zimbabwe, among 1230 pregnant women, 239 (19%) reported their partner had been HIV tested, of whom 213 knew partner results, and 8 reported a HIV positive partner (0.6% of overall cohort). Only 1 of 14 incident HIV infections in this cohort occurred in a woman in a known serodiscordant partnership (10). Similarly, in a Kenyan cohort of 1310 pregnant women, only 1% reported knowing their partner was HIV positive, and these women had *lower* risk of HIV infection than women with unknown or reportedly HIV negative partners (11). HIV risk may be lower among the select few women who report knowing their partner's HIV-seropositive status because these partners are already on ART or use condoms. Many women do not know their partner's HIV status or believe their partner is HIV negative (12).

As prevention of mother-to-child HIV transmission (PMTCT) programs expand, women with chronic HIV infection are diagnosed and receive antiretrovirals (ARVs) in pregnancy, which decreases mother-to-child HIV transmission (MTCT) to <1% (13). In contrast, women who test HIV negative during pregnancy, often feel reassured that they do not have HIV or HIV risk. If these women acutely acquire HIV, their risk of MTCT is very high. Without ARVs, acute maternal HIV has a 2-fold increased risk of MTCT compared to chronic HIV maternal infection, due to higher viral load and absent HIV immune responses (14). With ARVs, there is >5 to 15-fold increased risk of MTCT among mothers with acute HIV because ARVs are started late or after transmission has occurred, while mothers with chronic HIV have low MTCT due to timely ARVs (Figure 2) (2). With global PMTCT expansion, acutely infected mothers contribute an increasing proportion of infant HIV infections. Over 40% of new infant HIV infections worldwide are estimated to be due to maternal HIV acquisition in pregnancy and postpartum (15). As a result, mothers may only be diagnosed when their symptomatic child is diagnosed with HIV. Addressing PMTCT Prong 1 (primary HIV prevention in women) during the pregnancy/postpartum period is critical for achieving elimination of MTCT (16).

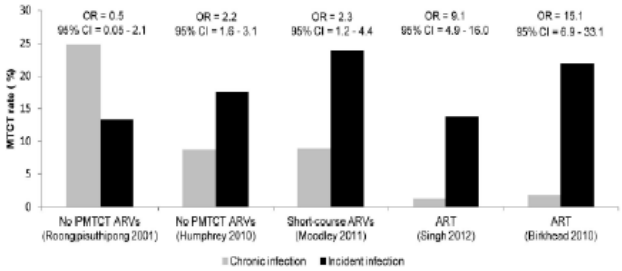


Figure 2: MTCT in acute vs chronic maternal HIV (2)

Identifying Women at Risk in Pregnancy

Clinical prediction tools combine clinical, examination and laboratory features to identify high-risk groups. Using data from three cohorts of HIV serodiscordant couples, a risk score was developed which incorporated information regarding marital status, partner HIV RNA load, partner circumcision, and age (17). The risk score was useful in identifying a subset (28%) of couples who contributed 67% of HIV infections. Among women at risk for HIV, data from the VOICE study, including variables such as age, STIs, and partner characteristics or partner support, were used to develop a score that identified 36% of women who contributed 66% of infections (18, 19). Both of these scores (i.e., for serodiscordant couples and for women at risk) have been pilots as standardized risk assessment tools to guide initiation of PrEP for HIV prevention.

For pregnant women, a risk scoring tool has also been developed to help identify those at greater HIV risk (20). This tool, developed and validated using data from 1,304 women living in Kenya, includes the following variables: Partner HIV status unknown, number of lifetime sexual partners, and history of syphilis. Women with a score >6 made up 16% of the population but accounted for 56% of HIV acquisition events.

For pregnant women, risk assessment alone may not identify all women at risk of HIV acquisition during pregnancy. Partner self-testing is a strategy that has been successfully used to identify previously unknown HIV-positive partners of pregnant women in Western Kenya. A recent study demonstrated high uptake of partner-testing when multiple self-tests are given distributed to women in antenatal care clinics along with instructions about how to use the tests and counseling about using discretion when determining whether to offer a self-test to sexual partners (21). Of women enrolled in the study, 91% (of 58 participants) reported distributing the self-test to their primary sexual partner *and* being present when their partner used the test (21). The strategy was also found safe for women who participated. This study did exclude a small number of women attending clinics who believed violence could occur from distributing the self-tests, who would likely benefit from PrEP given the risk of violence in their relationship. Including a self-testing intervention that increases partner self-testing will allow this study to identify women who may be categorized as low risk in the risk assessment but have a previously unknown HIV positive partner.

Pre-Exposure Prophylaxis (PrEP) and Women

As new studies examine topical microbicides and long-acting PrEP formulations for HIV prevention (22-25), oral PrEP remains a leading candidate for pregnancy given substantial evidence of efficacy, safety, and lack of potential for genital tract irritation that could precipitate preterm birth or ascending infection in pregnancy (26). Increasing partner ART use is another highly effective and complementary approach (27). Condoms, though effective, have not been widely adopted by pregnant/postpartum women, who are usually married and find it difficult to negotiate for condom use in the setting of a presumably stable relationship.

In the Partners PrEP study, sub-group analyses demonstrated high protective efficacy of oral TDF (71%, p<0.002) or TDF/FTC (86%, p<0.005) in women in serodisordant partnerships (28). Subsequent analyses of high-risk women in Partners PrEP (>5% incidence in placebo arm), demonstrated similar high PrEP efficacy (64-84%) (29). An adherence substudy of Partners PrEP found that PrEP efficacy greater than 90% with adherence over 80% by unannounced pill count or electronic pill bottle monitoring (30). Some enthusiasm for PrEP use in women faltered after two large RCTs (FEM PrEP and VOICE) failed to demonstrate efficacy (31, 32). Failure of PrEP in these trials was not due to lack of regimen efficacy but to non-adherence (33-35) (Figure 3). In both RCTs high-risk young women were receiving an as-yet unproven intervention or a placebo (36-38). In these studies, drug levels demonstrated low adherence, which differed from self-reported adherence.

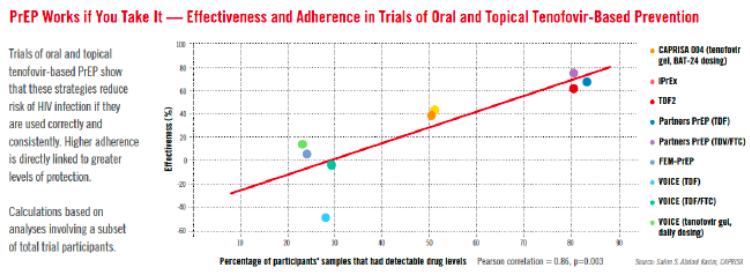


Figure 3: AVAC summary of PrEP efficacy and adherence

Emerging qualitative data provides insights on reasons for low adherence in some studies (37, 39). In FEM-PrEP desire to answer research questions and belief that PrEP could decrease HIV incidence facilitated adherence (34, 38, 40). Side-effects influenced non-adherence, while having an HIV positive partner increased adherence in the Botswana TDF-2 trial (41). Analogously, external partnerships were associated with non-adherence in Partners PrEP, while partner support and desire to preserve the partnership facilitated adherence (30, 42, 43). Concerns about efficacy and social stigma were noted as reasons for non-adherence in VOICE (44). In an unblinded setting with known effectiveness, PrEP motivation may be higher than in placebo-

controlled trials and this has been shown in demonstration projects (see B7) (37). In the context of pregnancy, women may have higher adherence than outside of pregnancy because of motivation to protect themselves and their infant and health system support.

In 'real-life' demonstration projects, participants have had high adherence and few HIV infections. As of June 2015, AVAC listed 37 demonstration projects on PrEP globally, including 14 that involve women, none of which is focused on PrEP in pregnancy. PrEP demonstration projects involving women have shown good adherence (>75%) in random drug level testing (Table 1). The Partners Demonstration project, which used PrEP as a bridge approach to ART in serodiscordant couples with a high risk score, observed an estimated 96% reduction in HIV transmission (45). The bridge approach provides dual protection to newly diagnosed serodiscordant couples with PrEP use until viral suppression occurs in the partner on ART. The bridge approach is ideal for the MCH setting, in which HIV negative women accessing pregnancy care can be the gateway to expedite HIV diagnosis and treatment of male partner HIV infection, which otherwise occurs late. For pregnant women in newly diagnosed serodiscordant couples PrEP will be essential for protection until partner ART is fully effective; however, prompt partner ART would shorten duration of PrEP with discontinuation when partners are suppressed. Sustained partner ART would decrease need for PrEP in subsequent pregnancies.

Table 1. PrEP demonstration projects in women show high effectiveness and adherence (45-47)

Setting, study	Number enrolled/ screened (%)	PrEP adherence (method)	# HIV infections	# Infections expected without PrEP
TDF2, Botswana; open label extension men and women	229/335 (86%)	93% TFV detected; 87% TDF in women	No HIV infections during 1 year	5-6
Partners Demonstration, Uganda, Kenya; Discordant couples with high risk score	1013 couples 96% uptake	>80% (TFV detection)	4 infections/1700 p-years f/u (95% reduction)	83
ADAPT, South Africa	191 women, different PrEP schedules	75% with daily PrEP (TFV/FTC levels)	NA	NA

Safety of PrEP in Pregnancy

Data on PrEP safety can be extrapolated a number of studies including PMTCT and ART research, which includes TDF and FTC use in pregnancy (48-53). In infants of HIV-infected women receiving TDF and FTC there has been limited signal of fetal risk – the lack of increased risk in this group with concurrent exposure to other ARVs and maternal HIV is reassuring (51). The Antiretroviral Pregnancy Registry database includes data from 1982 infants exposed to TDF in first trimester in the US, without evidence of congenital anomalies (54). There has been evidence of small growth deficits and decreased neonatal bone mineral content (5.3 gm lower) among infants receiving PMTCT-TDF, but clinical relevance of these findings is unknown (53, 55). There is also a growing body of evidence from studies of conception among serodiscordant couples and PrEP RCTs that show no adverse events or difference in outcomes among infants born to mothers using PrEP at conception of during pregnancy (56-60).

In the Partners PrEP trial, women who became pregnant on PrEP had no evidence of adverse infant outcomes or long-term growth (56). Among 431 women who became pregnant, pregnancy outcomes were similar between placebo and PrEP arms. Among 167 infants with serial growth assessment, there were no differences in weight or height z-scores or head circumference during infancy between infants with in utero PrEP vs. placebo, However, women discontinued PrEP when pregnancy was diagnosed resulting in limited pregnancy time on PrEP. While safety data

are generally reassuring, there is need for continued accrual of data on growth and pregnancy outcomes in PrEP research studies and demonstration projects. Breastfeeding is not a contraindication for maternal PrEP as minimal drug is likely to pass to infants, however, there are scant data from infants exposed to PrEP during lactation (61-63).

During the past decade, legal, ethical, and policy deliberations have informed a vision to accelerate access to effective interventions for pregnant women and their children (64). Pregnant women currently receive several preventive interventions, including anti-malarials, PMTCT, and TB-prevention (if HIV infected). For some interventions (malaria prophylaxis and early PMTCT), pregnancy implementation was informed by RCTs conducted in pregnant women and their infants with most benefits for the infant. For other interventions (isoniazid in HIV-infected women), efficacy evidence was extrapolated from non-pregnant adult studies and safety data was obtained from observational studies. The level of safety evidence for PrEP (no animal fetal toxicity, thousands of infants exposed to TDF/FTC PMTCT, hundreds to PrEP in early pregnancy) led WHO, CDC, and the Kenyan Ministry of Health (MoH) to permit PrEP use in pregnancy (61, 65, 66). WHO early-release guidelines (Sept 2015) recommend PrEP for anyone at 'substantial HIV risk', and noted need for research on PrEP in pregnancy and lactation (66), and updated WHO guidance from 2017 recommended the use of PrEP in pregnancy and lactation, although important safety and implementation gaps remain. Implementation science studies can provide a framework to increase accrual of safety and effectiveness data of PrEP in pregnancy while refining programmatic strategies.

8) RATIONALE

In a region with 15-20% HIV prevalence, an estimated 20% of HIV-uninfected women could have HIV exposures in pregnancy. In a theoretical scenario of perfect PrEP coverage, all women at risk receive PrEP while no women not at HIV risk receive PrEP (Figure 4). With mandatory PrEP given to all women (similar to the approaches used for malaria prophylaxis), all women at risk would be covered but many women not at risk receive unnecessary PrEP. Our premise is that a targeted PrEP model may be closer to perfect coverage than a universal offer/self-select model. Implementing targeted PrEP through strategies that include facilitation of partner testing with self-tests could add HIV prevention benefit by increasing partner HIV diagnosis and treatment similar to the initiation of PrEP among pregnant women. By implementing these strategies and measuring uptake, process, and HIV incidence, we can inform the best health systems model for PrEP delivery in pregnancy.

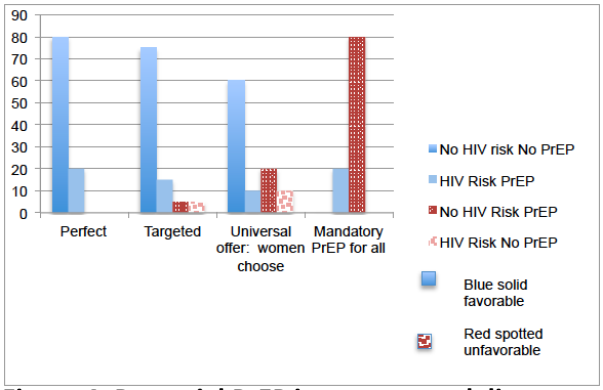


Figure 4: Potential PrEP in pregnancy delivery strategies

9) HYPOTHESIS & STUDY QUESTIONS:

In this study, we hypothesize that PrEP can be implemented in antenatal care clinics in Kenya such that PrEP will be acceptable and used by women at risk of HIV acquisition during pregnancy.

a) BROAD OBJECTIVES

The broad objective of this study is to determine the best model for optimized PrEP delivery in pregnancy by using existing highly accessed MCH systems as a platform for efficiently delivering PrEP to pregnant women.

b) SPECIFIC OBJECTIVES

AIM 1a. In a cluster RCT among HIV-uninfected pregnant women, to compare universal PrEP (offered to all; women self-select PrEP) to targeted PrEP (offered to women with a high risk score incorporating available partner HIV self-test data) for outcomes reflecting the balance of PrEP effectiveness avoiding unnecessary PrEP exposure to women at low or no risk of HIV: HIV incidence at 9 months postpartum among all women (including those who did and did not receive PrEP) and proportion of women exposed to PrEP.

- *Hypothesis: Because of better matching of PrEP and targeted, specific PrEP counseling, use to HIV risk, targeted PrEP will result in lower HIV incidence and optimized proportion of women on PrEP.*

AIM 1b. To compare universal versus targeted PrEP arms for proportion of all women on PrEP, proportion of women 'appropriately' on PrEP (based on risk factors), PrEP adherence (drug levels), PrEP duration, partners with HIV status, partners on ART, and infant birthweight, preterm birth, and growth curves; to compare infant outcomes in PrEP exposed infants vs. unexposed; and to determine cofactors of maternal HIV incidence overall and stratified by trial arm.

- *Hypotheses: Targeted PrEP will result in more 'appropriate' PrEP use, better adherence, shorter PrEP duration (stop after partner viral suppression), more partners on ART, and similar infant outcomes.*

AIM 2. To estimate the incremental cost-effectiveness of targeted PrEP compared to universal PrEP for women during pregnancy and in the postpartum period, per incident HIV infection and disability adjusted life year (DALY) averted.

- *Hypothesis: Targeting PrEP to women at highest risk of HIV acquisition will be more cost-effective than universal PrEP provision.*

AIM 3. To qualitatively assess barriers and facilitators to adherence, acceptability, feasibility and potential adaptations in all 3 RCT arms at the organizational, provider, and individual woman level.

- *Hypothesis: Both models will be acceptable to women and providers; organizations will prefer targeted PrEP.*

10) STUDY DESIGN AND METHODOLOGY

This is a mixed-methods cluster randomized study. The study has two components which will be rolled out with component 2 beginning once enrollment in the cluster RCT is underway:

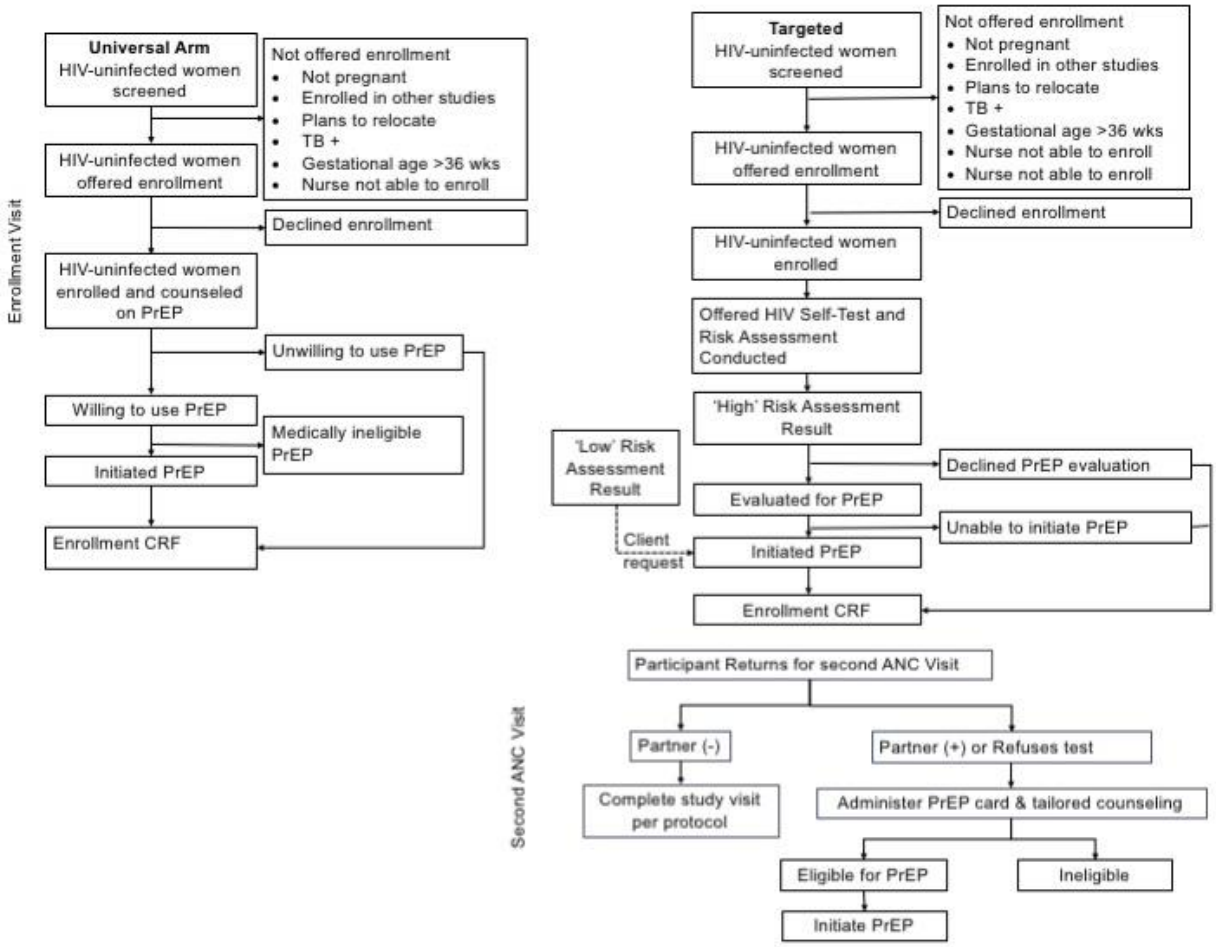
- **Component 1**: This study is a cluster RCT, with economic and quantitative data collection, which will inform the identification of a cost-effective PrEP delivery approach for pregnant women.
- **Component 2:** Qualitative evaluation assessing barriers and facilitators to PrEP uptake at organizational, facility and individual women levels.

a) STUDY AREA DESCRIPTION:

The proposed study will be conducted in twenty health care facilities in Kisumu, Homa Bay, and/or Siaya Counties, Kenya. Facilities will be selected based on the HIV seroprevelance and ANC volume. Facilities will be selected for inclusion if they are located in a region with 15-20% HIV seroprevalence, have approximately 500+ HIV-negative clients receiving antenatal care at the facility per year, and offer postnatal care services including infant immunizations. If possible, facilities will also be excluded if they do not have an onsite Comprehensive Care Clinic (CCC) to ensure appropriate linkage to care for male partners identified as HIV-positive through partner testing. Facilities will also be excluded if they do not have the capability to conduct antenatal

syphilis testing, either via RPR/VDRL or dual HIV/Syphilis test depending on MoH guidance. An overview of all enrollment procedures is shown in Figure 3 and the follow up visit schedule is included in Figure 4.

Figure 3: Overview of study procedures



Follow Up Visit Schedule

		Weeks gestation						Weeks/months postpartum			
		<20	20-24	25-28	29-32	>32	Birth	6 wk.	14 wk	6 mo	9 mo
Visit schedule based on gestational age at enrollment		E	F	F	F	F		F	F	F	F
			E	F	F	F		F	F	F	F
				E	F	F		F	F	F	F
					E	F		F	F	F	F
						E		F	F	F	F
Procedures	HIV test	At enrollment, any gestage				X		X	X	X	X
	DBS*	1-mo PrEP FUP visit, any gestage						X		X	X
	PrEP refill*	1-mo PrEP FUP visit, any gestage						X	X	X	X

E = enrollment visit, F = FUP visit, * Only for women who initiate PrEP
Note: Women who enroll 33-35 weeks may have an additional FUP visit prior to birth. For example, if a women enrolls at 33 weeks, she would have a follow up visit at 37 weeks and then resume the standard postpartum schedule.

COMPONENT 1: CLUSTER-RANDOMIZED CONTROL TRIAL

a) STUDY DESIGN

We will select 20 clinics from Western Kenya. Ten clinics will be randomized to universal PrEP and ten to targeted PrEP (Table 2). To ensure balance between study arms in terms of key site characteristics, sites will be categorized on HIV prevalence and ANC volume, and restricted randomization will be used for site (cluster) allocation to intervention and control arms (67). Specifically, all possible randomizations that evenly distribute sites on these two specified factors (HIV prevalence, ANC volume) into 2 study arms will be generated, and one combination will be selected using a random number generator. Randomization and allocation will be performed by Dr. Richardson, who has no knowledge of sites other than the variables included in the restricted randomization process.

Table 2: Difference between Universal and Targeted PrEP arms

	HIV self-test for partners	Risk score used to guide PrEP offer	Universal PrEP Counseling	Enhanced PrEP counseling that communicates individual risk	Data on partner HIV status
Universal			X		
Targeted	X	X		X	X

b) STUDY POPULATIONS

At each clinic, enrollment will occur over an approximately 10-month period (~20 HIV negative women enrolled per month) with a ~1-year period of follow-up to 9 months postpartum (time of routine measles immunizations). Eligibility for enrollment will include age ≥15 years, pregnancy, and tuberculosis negative, plans to reside in area for at least one year postpartum, plans to receive postnatal and infant care at the study facility, and are not currently enrolled in any other studies.

c) SAMPLE SIZE DETERMINATION AND FORMULAS USED

Table 3: Sample size power calculations

k	HIV incidence universal	HIV incidence targeted	# women per clinic	#clinics per arm	Total # women
0.2	4%	2%	50	27	2700
0.2	4%	2%	100	15	3000
0.2	4%	2%	150	12	3600
0.2	4%	2%	200	10	4000
0.2	4%	2%	250	9	4500
0.2	4%	2%	300	8	4800
0.2	4%	1.3%	200	6	2400

Restricted randomization will be used to ensure that the two arms of the trial have balance in terms of prevalence of HIV, ANC volume, and rates of partner disclosure at included clinics (based on data from our prior CHIME evaluation of 141 MCH clinics). Assuming a coefficient of variation (k) of 0.2, the study has 80% power to detect a 2-fold difference in HIV incidence (between 4% and 2%) with 10 clinics per cluster and at least 200 women per cluster (Table 3). If targeted PrEP resulted in much better performance (67% decrease rather than 50%), 6 clinics per cluster would be sufficient. Deriving our sample size from HIV incidence difference is conservative and will enable ample statistical power to detect effects on other outcomes (such as proportion on PrEP and partner characteristics). Table 4 outlines implications of potential RCT outcomes illustrating the value of data regarding the two PrEP delivery models in scenarios with

or without a significant difference in HIV incidence. We anticipate that the targeted arm may have 20% of women receiving PrEP (based on MSS risk score estimates) while the universal PrEP arm may have 5-25% of women requesting PrEP, however, these are speculative estimates. The study may not detect a difference in HIV incidence between PrEP delivery models because of appropriate PrEP uptake and use in both. However, as outlined in the contingency table (Table 4), for all scenarios the RCT would yield important data on viable approaches for delivering PrEP in pregnancy and likely reveal a superior model in terms of the balance of effectiveness, safety, acceptability, feasibility, and cost-effectiveness.

Table 4: Contingency Table Demonstrating Implications of Potential RCT Outcomes

	Potential HIV incidence outcome	Other potential results	Impact on programs policy in high HIV prevalence regions	Programmatically relevant data from study
Hypothesis Proved	Targeted better	Fewer women on PrEP, cost-effective, safe	Implement targeted PrEP	Data to model and compare impact on HIV transmission, cost, and scale up. HIV incidence/CI, cost-effectiveness, safety, feasibility, process
Hypothesis opposed	Universal better	Fewer women on PrEP, cost-effective, safe	Implement universal PrEP	
Mixed benefits	Universal better	Universal too many women on PrEP not cost effective	Refine universal strategy to decrease cost and unnecessary PrEP exposure	
Mixed findings	Incidence low in both, no difference	Targeted more cost-effective results in few on PrEP	Implement targeted PrEP	HIV incidence estimate/CI, cost-effectiveness, safety, process
		University more cost-effective and fewer women on PrEP	Implement universal PrEP	

d) RECRUITMENT PROCEDURES

Following routine antenatal HIV testing during an antenatal care (ANC) visit, the study nurse will recruit HIV seronegative women and determine eligibility. Following screening consent, a brief screening form will capture age, gestational age, and eligibility characteristics. For women identified as eligible for the study, we will obtain written informed consent for participation and the women will be enrolled. The informed consent will emphasize that participation in this study is completely voluntary and will not affect their ability to receive antenatal, delivery or postnatal care at this or any other facility. This study will utilize two versions of the consent form, one used in universal PrEP counseling facilities and one used in targeted PrEP counseling facilities to explicitly describe the facility-specific procedures participants will undergo. A screening & enrollment log will capture the proportion of women screened, deemed to be eligible, and eventually enrolled, to determine the ratios of clinic attendees:screened and eligible:enrolled, which will aid in estimates of generalizability. We will also collect data from each facility on the total number of ANC attendees per month.

e) STUDY PROCEDURES

Enrollment data collection:

Enrollment for all study participants will include a detailed questionnaire, including assessment of demographics, mental health, social support systems, drug and alcohol use, risk perception, risk score, partner HIV status, education, prior obstetric history, education, marital status and income. Data from the MCH card will be abstracted, including confirmation of HIV results as well as results

of antenatal syphilis testing. As is standard of care in MCH clinics, in both trial arms a referral letter encouraging HIV testing will be provided for women to give to partners and clinic-based HIV testing will be available for any male partner seeking testing.

Universal PrEP Clinics, Enrollment Visit (N=10):
Counseling at universal sites, will use a standardized counseling script to state that PrEP is available for women at risk for HIV, explain that HIV prevalence in the region is high, and will note that women with HIV positive partners or who don't know their partner's status may be at risk. Counseling will specify that women may have their own reasons to feel at risk or to want PrEP. Following standardized counseling, women will select PrEP at the same visit or will be allowed to deliberate on the decision and come back at the next visit with a decision. Women will be informed that it is advisable to use PrEP if they know their partner is HIV positive or if they do not know their partner's status and will be encouraged to bring untested partners to clinic if status is unknown. Women who select PrEP will be welcome to involve their partners in counseling regarding PrEP and those with recently diagnosed HIV positive male partners (via the clinic referral system) will linked to care following the facilities standard linkage to care procedures.

Table 5: Risk Score Card for HIV acquisition in pregnancy

Risk factor	Value per factor	Score
No. of lifetime sexual partner		
1 point per sexual partner	Enter at least 1	
Male partner HIV status		
Male partner HIV status known or no male partner	0	
Male partner HIV status unknown	6	
Syphilis		
nonreactive	0	
reactive	5	
	Total risk score	

Targeted PrEP Clinics, Enrollment Visit (N=10):
Following informed consent and enrollment data collection, the targeted PrEP clinics will provide two inter-related innovations: risk assessment-informed PrEP counselling and partner HIV Self-Test counselling.

Risk Assessment and PrEP Counselling:
The results of the PrEP risk assessment will be used to guide PrEP counselling and the offer of proceeding to the PrEP card-based eligibility assessment. Participants who score greater than 6 on the risk assessment will receive additional PrEP counselling that includes information about specific risk factors tailored to the participant (Table 5). These participants will then elect whether to proceed to the PrEP card eligibility assessment. Women who score 6 or less will not be individually counseled about PrEP. However, if they ask for PrEP they will enter the clinical assessment pathway and can be prescribed PrEP if found to be clinically eligible. We anticipate that participants with known HIV-positive partners will self-select for the PrEP eligibility assessment. Women who request PrEP despite not meeting the targeted PrEP criteria will be identified and approached for in-depth interviews to better understand their choices in Component 2 of the study.

Partner HIV Self-Testing:
Women will be offered HIV self-test kits to take to their partner for HIV testing. This will be used to provide further information on partner HIV-status: either initiate women in previously unidentified serodiscordant couples on PrEP at subsequent study visits, or to discontinue PrEP

for women who are able to confirm their partner's HIV-negative status. All women will be offered two self-tests so that they can take the test at the same time as their partner, if they chose to do so. If a woman does not receive the self-test counseling during the first study visit, they will receive self-testing counseling during their next study visit.

Trained program staff will counsel study participants in the use of self-testing kits including. First, they will assess whether the women believe violence could occur when providing the self-testing kit to their partner. If a woman declines the self-testing kit or fears violence, they will not receive the testing kit and this information will be included in the targeted PrEP administration algorithm.. Women who are comfortable providing a self-test to their sexual partner(s) will be instructed by study staff on the use of an oral fluid based rapid HIV test (OraQuick Rapid HIV-1/2 antibody test, OraSure Technologies, Bethlehem, PA, USA). Study staff will demonstrate how to use the oral self-testing including opening the package, collection of fluid samples, waiting 20-minutes before reading the test, and reading test results. Women will be counseled that it is entirely their choice as to whether to offer a self-test to their partner. Participants will be provided with a one-page summary document that describes the self-testing methods and provided information on receiving confirmation testing and linkages to care in the event their partner(s) test positive. Women will be asked to return to the clinic at their next antenatal care visit to report on the results of their partner's self-test.

DBS collection for confirmatory HIV testing
DBS will be collected using a finger stick from all participants at enrollment and stored for future confirmatory HIV testing should a client seroconvert while in the study. Blood from the finger stick will be placed onto five circles on labeled DBS card and allowed to dry between 2-hours and overnight before storing in a low gas permeability plastic bag with a humidity indicator and stored in a freezer between -20 and -80 degrees at CDC KEMRI laboratory for future assessment.

Targeted PrEP Clinic, Visit 2 (next scheduled antenatal care visit):
During the second study visit, participants will report the results of their partner's self-test. Partners who are identified as HIV-positive through the self-testing will be referred for HIV confirmatory testing and treatment at the nearest CCC, ideally located in the same facility if possible. Women who report that their partners refused the self-test, did not share the results of their self-test, or were unable to take the test will receive additional PrEP counseling during the second study visit, using the same standardized script as high-risk women identified in the first study visit. Women who do not return for the scheduled study visits or to obtain test results will be contacted by study staff.

PrEP Initiation, Universal and Targeted Arms
Women who elect to start PrEP will receive point of care hepatitis B (HBsAg) and creatinine (Cr) testing. Women who are HBsAg positive or who have estimated creatinine clearance (CrCl) $\leq$50 ml/min will be medically ineligible to initiate PrEP per NASCOP guidelines below.

PrEP Medications
PrEP medication and dosing will follow the 2016 Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infections in Kenya using the preferred oral TDF/FTC (300mg/200mg) once per day (66).

Follow Up Visits, Universal and Targeted Arms
All participants:

Women will follow the MCH schedule for their routine ANC and postpartum/immunization clinic visits. Study visits will be performed at all subsequent ANC visits and the 6-week, 14-week, 6-month, and 9-month postpartum visits, the visit schedule is outlined in table 4. All women will receive HIV rapid test at follow up visits. The study visits are designed to meet MOH guidelines for PrEP users to receive HIV testing and adherence counselling every three months. Data on risk assessment, partnership characteristics, sexual activity and contraception use, and sociobehavioral factors may be collected at all study visits. Additional data will be collected on infant growth, birth weight and estimated gestation at birth or diagnosed preterm birth (for women who deliver at facilities) and serial growth will be abstracted from MCH cards; z-scores will be calculated using WHO Anthro-Plus. Data on birth outcomes (stillbirth, miscarriage, mortality, congenital anomalies) and birth length will be abstracted from MCH card or interview. We may also collect a small amount of hair from participants and their babies (50 strands).

Follow up Adherence Counseling at both universal and targeting PrEP counseling sites:
Among women who start PrEP, instructions on use of drug and counseling to optimize adherence will be identical between targeted and universal clinics. Experienced counselors from Partners PrEP demonstration projects will provide training and feedback to nurses at study sites prior to initiation of RCT. Maternal creatinine will be obtained annually and CrCl estimated. PrEP will be discontinued if estimated CrCl is ≤50 ml/min. Any drug-related reactions or adverse events will be documented and summarized in weekly meetings (pooled).

PrEP Adherence:
We will use a combination of self-report and tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) in red blood cells from dried blood spots to assess PrEP adherence. DBS will be collected from all women on PrEP at all subsequent antenatal visits and at weeks 6, 14, and 6 and 9 months postpartum (Table 6). DBS will be collected using a finger stick. Blood from the finger stick will be placed onto five circles on labeled DBS card and allowed to dry between 2-hours and overnight before storing in a low gas permeability plastic bag with a humidity indicator and stored in a freezer between -20 and -80 degrees at CDC KEMRI laboratory for future assessment of TFV-DP and FTC-TP in red blood cells (Standard Operating Procedure from the Anderson Lab attached).

We may also collect a small amount of hair from participants and their babies (approximately 50 strand) to measure long-term adherence to PrEP at the same follow up time points as DBS. This will let us know whether a mother has been taking PrEP for the past few months. Hair will be sent to the University of California, San Francisco (UCSF) Hair Analytical Laboratory to perform this assay as it is one of the only labs available who perform this test. This test is not yet available in Kenya.

These measures of adherence will be helpful in analyzing short-term (DBS, currently approved) and long-term (hair) PrEP adherence.

Seroconversion
Women who seroconvert will be managed according to NASCOP guidelines. Point-of-care PCR testing may be used where available to investigate potential seroconversions.
PrEP Discontinuation:
PrEP will be discontinued if (1) participant seroconverts during the study; (2) participants risk status changes (e.g. a partner who previously refused or was unable to take the self-test tests negative); (3) renal dysfunction with creatinine clearance <50ml/min; (4) client requests to stop; (5) sustained non-adherence; or (6) participant reports their HIV-positive partner has achieved

sustained viral suppression. Reasons for discontinuation will be documented, participants will be requested to return for 6-week, 6-month, and 9-month postpartum HIV testing, and counseled on other risk reduction strategies. If a participant seroconverts during the study period, they will be linked with care at the nearest CCC.

Compensation:
Compensation schedule will be dependent on number of required study visits. All study participants will receive Ksh 300 at all study visits to compensate for their time and transportation expenses to participate in the study.

Table 6: Study Visits and specimen collection schedule

	Pregnancy					Postpartum			
	Repeated ANC Visits					Wk 6	Wk 14	Mo 6	Mo 9
Routine MCH Schedule	X	X	X	X	X	X	X	X	X
Study Visits- All Facilities		X				X		X	
Consent for the study	X								
CRFs administered	X	X	X	X	X	X	X	X	X
HIV test for all participants	X	*	*	*	X	X	X	X	X
DBS collection for all participants for confirmatory HIV testing	X								
DBS Collect for all participants on PrEP		X	X	X	X	X	X	X	X
MCH Card data abstraction	X	X	X	X	X	X			X
Partner referral letter from MCH	X								
Birth outcomes, growth						X	X	X	X
Decision re: PrEP		X	X	X	X	X	X	X	X

*HIV Test administered at one-month follow up visit for all participants

Health Economic Evaluation Activities:
The following data will be collected for the CEA: (1) estimating the cost of the intervention; and (2) the number of participants initiated on PrEP, HIV incidence at 6-weeks and 9-months postpartum, and PrEP adherence, which will be derived from the study. In addition, the base case costs of facility-based care will be estimated and sensitivity analyses will be conducted. Cost data will include: (1) Conversion rate of local currency (Kenyan Shilling) to U.S. dollars at 6-month intervals over the life of the project; (2) costs of all commodities used in the intervention; (3) labor costs for intervention workers; (4) average time clients spent with intervention including transportation / staff time / time for referrals; (5) local wages of target population; (6) rent; (7) maintenance; (8) volunteer activities; (9) user fees; (10) value of donated goods and services; and (11) other relevant costs, including training of providers and mobile van, fuel costs for community-based delivery.

Time and motion studies will be conducted to determine the time and resources necessary to provide PrEP counseling in pregnancy, monitoring, and resupply. Time and motion studies will be conducted over a two-week period at each site during study initiation and again when the intervention is running at full capacity. An experienced research assistant will collect data on the time required to complete each step of the intervention. Results from initial time and motion studies will be shared with the teams and strategies for efficiency shared to reduce the time needed for the intervention. Observing multiple visits will allow estimation of the average time taken for each step; the time take for research purposes (e.g. data collection) will be noted separately from the estimated time needed for clinical services. Interviews with study staff will also quantify the effort required for each step of community-based HIV care. Through time and motion studies the number of participants who could be supported by a clinic will be estimated.

A discount rate of 3% will be used with sensitivity analysis of 0% to 5%. Additionally, for analysis taking the societal perspective we shall also include the cost to clients in terms of lost time, wages, childcare, and other relevant opportunity costs. To assess these issues, we will ask participants what expenses and opportunity costs they incurred to receive the interventions in the surveys already planned for the project. We will also collect data on the average cost of medical care in Kenya associated with pregnancy, postpartum, HIV infection and AIDS through literature review.

Cost data will be used with study results and mathematical models of HIV transmission to estimate the population level effectiveness and cost-effectiveness of the intervention. The models will use de-identified study data.

Future contact with subjects
Participants will be asked if they would be willing to be contacted in the future about participating in another study about PrEP after exiting from PrIMA. Participants who agree to be contacted will sign a consent addendum. Women will be re-contacted via phone.

f) LABORATORY METHODS

Hepatitis B (HBSAg) and Creatinine (Cr) testing: All participants in universal and targeted PrEP facilities who elect to use PrEP will be tested for Hepatitis B and creatinine levels using point of care tests.
PrEP Adherence Methods: A subset of DBS specimens (5-10%; estimated total 440 specimens) from all women on PrEP will be randomly selected for TFV-DP and FTC-TP levels. DBS TFV levels will be conducted at Dr. Peter Anderson's laboratory (using liquid chromatography/tandem mass spectrometry) at the University of Colorado. The presence of detectable FTC-TP will be a proxy for recent adherence in the preceding 48 hours. Given a half-life of 17 days for TFV-DP in DBS, levels of TFV-DP per punch can approximate cumulative dosing (<349 fmol/punch, <2 tab/week; 350-699 fmol/punch 2-3 tabs/week, 700-1249 fmol/punch 4-6 tabs/week, and 1250

fmol/punch (daily dosing) (69). The levels used in this analysis will be updated, as appropriate, if evidence emerges that other levels are more predictive.

g) DATA COLLECTION INSTRUMENTS

Paper copies of data collection tools for surveys are submitted with this application for human subjects review. They include:

- Screening Form
  - Age
  - Gestational Age
  - HIV-status
  - Plans to stay in the area for at least a year
- Enrollment questionnaire, including:
  - Demographic information (education, obstetric history, marital status, income)
  - Risk Perception Assessment
  - Risk Score Card
  - Partner HIV status
  - Self-Efficacy
  - Social Support and Mental Health
  - IPV assessment
  - Partner Characteristic
  - PrEP attitudes and acceptability (HIV/PrEP Stigma Assessment)
- ANC Card Abstraction form
  - HIV status
  - Gestational Age
  - Maternal Age
  - Syphilis
  - TB status
- PrEP Counseling Outcomes form
- Partner self-test results
- MCH Card Abstraction Form, including:
  - Infant length
  - Birth weight
  - Gestational age at birth
  - Serial growth
  - Stillbirth
  - Neonatal mortality
  - Miscarriage
  - Infant congenital abnormality
- Infant, neonatal and maternal mortality (including WHO verbal autopsy instrument)
- Maternal follow up
  - HIV-status 6-weeks postpartum
  - 14 weeks postpartum
  - 6-months postpartum
  - HIV-status 9 months postpartum
  - Hepatitis B Antigen test result
  - Creatinine level test result
  - Sexual activity and contraceptive use
- PrEP Adherence
  - Pill Count data

  - Self-Assessment
  - DBS collection methods
  - Discontinuation Documentation
- Health Economic Evaluation
  - Incremental costs at facility level, including costs incurred and averted
  - Costs incurred at participant level interview form
  - Time and motion data collection form

h) VARIABLES: Outcomes, indicators, and source documents

Table 7: Variables: Outcomes, Indicators, and source documents		
	Indicator	Source
Primary Outcomes		
Maternal HIV, 6-weeks pp	HIV Rapid Test	Study Visit, maternal specimens
Maternal HIV, 9-months pp	HIV Rapid Test	Study Visit, maternal specimens
PrEP Exposure	Number received PrEP/All Participants	PrEP Counseling outcome form
Secondary Outcomes		
Appropriate PrEP Use	Scored 1 for high risk women using PrEP and low risk women not using PrEP; 0 for high risk women NOT on PrEP and low risk women using PrEP	PrEP Counseling outcome form
PrEP Adherence	TFV/DP and FTC test results from 440 randomly selected specimens	Dried Blood Spots
PrEP Duration	Number of days on PrEP	Self-report captured on adherence counseling form; pharmacy records
Partners HIV Self-test	Partners Self-test result	self-report
Infant Birth weight	Birth weight	MCH card
Preterm Birth	Estimated gestational age at birth	MCH card
Infant Growth	Infant height, weight, and age for WAZ, HAZ, and WHZ Z-scores	MCH card
Cost Effectiveness Analysis Outcomes		
Costs Incurred	Costs for startup activities, service delivery, lab monitoring, PrEP support, PrEP	Cost Collection form
Time and Motion	Time for counseling, clinical procedures and PrEP counseling	Team and motion data collection form
Other Variables		
Age	Maternal Age	Self-report; or MCH Card
Age Discordance	Age Difference between participant and partner	self-report
Partner HIV Status	Positive, Negative, Unknown	Enrollment questionnaire
Sexual Behavior	Number of partners	self-report
Hepatitis B	Hepatitis B Antigen Negative	POC test at enrollment
Maternal Syphilis	RPR Test results (nonreactive/reactive)	MCH card; POC test
TB Status	TB test results	MCH card

j) QUALITY ASSURANCE PROCEDURES

Clinical Care: the study will adhere to Government of Kenya (GoK) guidelines for the care of pregnant/postpartum women and their infants; no clinical care will be provided by study staff. Data collected as part of the study will be abstracted from the mother's "Mother and Child Health booklet" and patient file, as well as the MCH clinic's medical records, in addition to questionnaires administered to participants. Counseling and testing for HIV will be performed in accordance with government-approved MCH guidelines. Study participants will receive their PrEP medicines in the MCH clinic where they receive ANC/PNC services.

Adherence to protocol: Weekly reporting of enrollment, follow-up, medical complications, laboratory results and specimen collection will enable us to monitor that the study is running according to approved protocols. Frequent reporting will also enable us to respond quickly to any problems that arise during the study.

Laboratory quality control: KEMRI/CDC Laboratory that will process specimens and conduct most of the laboratory tests are ISO certified, and participants in external quality control verification. For rapid HIV testing of study participants at enrollment and follow up, creatinine, and Hepatitis B testing, we will use point of care tests that have been approved by the Kenyan Ministry of Health (MoH). Standard laboratory QA/QC procedures will be conducted.

Data Quality: A dedicated data team will be responsible for data collection using an electronic data collection platform, ODK. The data team will communicate frequently with the *Administrative* and *Biostatistics Cores* for weekly and EAP reporting, data cleaning, study monitoring, and interim analyses.

k) TRAINING PROCEDURES

Dr. John Kinuthia will supervise training of clinical personnel and study staff in study procedures. This will include research ethics, HIV counseling and testing, PrEP Counseling, rapid HIV testing, specimen collection, and completion of surveys. Dr. Ruanne Barnabas will train study staff in costing methods including data collection tools, and time and motion study procedures. Dr. Harsha Thirumurthy will train study staff in self-testing counseling and protocols.

COMPONENT 2: Qualitative assessment at organizational, facility and individual levels

a) STUDY DESIGN

To comprehensively probe the uptake, acceptability and feasibility of universal versus targeted PrEP use strategies, we will use mixed methods to evaluate barriers and facilitators of PrEP uptake and use among women and their male partners, implementation facilitators and barriers among healthcare providers and community and country leaders (Table 8). We will conduct focus group discussions (FGDs) with healthcare workers and individual interviews with women and country and community level leaders. Interviews will inform development of a structured questionnaire to further assess barriers and facilitators of PrEP use. Better understanding the personal, interpersonal, social and logistical factors influencing PrEP use decisions and behaviors can inform the design and implementation of PrEP programs.

Table 8: Stratified Purposive Sampling Scheme and Topics for In-Depth Interviews						
In-Depth Individual Interviews						
Women: high-risk; No PrEP	Women: Low-risk; PrEP	Women: High Adherence	Women: high-risk; low adherence	Women: High-risk; high adherence	Male Partners	Community Leaders
Up to 20	Up to 20	Up to 20	Up to 20	Up to 20	Up to 15	Up to 10
Topics in interview						
• Personal HIV risk perception • Partner communication strategies and behaviors • Knowledge, attitudes and beliefs about PrEP • Reasons for uptake/refusal of PrEP or HIV testing • Barriers and facilitators of PrEP use and adherence				• Knowledge, attitudes and beliefs about PrEP • Barriers and facilitators of implementation • Suggestions for improved delivery		

b) STUDY POPULATION

Female In-Depth Interview (IDI): We will conduct IDIs with five categories of women based on their risk status and PrEP usage during the study: (1) high risk women who declined PrEP; (2) low risk women who accepted PrEP; (3) women with high adherence at ~9 months postpartum; (4) women with high risk but low adherence at ~9months postpartum; (5) women with high risk and high adherence at ~9 months postpartum. We will invite 90 women to participate in IDIs to understand reasons for PrEP usage during pregnancy and postpartum (Table 8). Women selected based on their acceptance or non-acceptance of PrEP will be recruited and interviewed early in the study, as close to when they made their decision about PrEP usage as logistically possible. For the purposes of these IDIs low risk women who accept PrEP will be defined as low-risk women in the universal PrEP facilities who accept PrEP or women in targeted PrEP facilities who do not meet the requirements for PrEP counseling but request PrEP. These IDIs will be instrumental in understanding whether the intervention did or did not work, why it did or did not work, and possible recommendations for enhancement of the intervention.

Male Partner IDI: We will conduct IDIs with partners who are referred by intervention arm study participants. Male partners will be identified by asking participants if they would be interested in referring their male partner to participate in an interview. Only women whose partners know about their participation in the RCT will be eligible for study participation. Up to 20 male partners will be interviewed. This approach will be helpful in understanding perceptions of the intervention in terms of benefits to care for mother and child, experiences with partner-initiated self-testing, and use of PrEP during pregnancy.

Community Leader IDIs: After the RCT, we will also conduct IDIs with 10 community leaders to understand community perceptions around PrEP use during pregnancy and postpartum as well as understanding community sentiments of the different approaches to PrEP counseling in facilities.

Provider Focus Group Discussion (FGD): We will conduct 4 FGDs of 7-10 participants each designed to capture provider perspectives on implementing targeted or universal PrEP counseling as part of antenatal care. We will also assess provider perspectives on partner self-testing counseling as part of antenatal care.

Female Surveys: Upon completion of the RCT, 600 participants, 30 per facility, will be randomly selected to participate in a structure exit interview based on the themes identified from the

qualitative interviews and focus group discussions. The exit interview participants will be identified before their final study visit and invited to participate in the survey during their final study visit. This will enable a quantitative frequency assessment of the most common themes.

c) SAMPLE SIZE DETERMINATION AND FORMULAS USED

We plan to conduct up to 90 semi-structured one-on-one interviews with women (10-20 women per stratified sample), 15 interviews with male partners, 4 focus group discussions with healthcare workers (2 FGDs per study arm), and 10 interviews with organizational level experts including those from the MOH and leaders in the community (Table 6). Based on prior experience conducting similar qualitative research, we believe that this sample size will reach data saturation (70,71).

d) RECRUITMENT PROCEDURES

Female PrEP Acceptance IDI: During antenatal and early postnatal care visits, study staff will approach women based on their risk status and whether they accepted PrEP to describe the purpose of the IDIs and invite interested women to participate. Participation in qualitative interviews will be included during study enrollment and informed consent process.

Female PrEP Adherence IDI: During the study, study staff will approach women based on their self-reported adherence to PrEP to describe the purpose of the IDIs and invite interested women to participate. Participation in qualitative interviews will be included in the during study enrollment and informed consent process.

Male Partner IDI: During study visits, we will sample women and ask them if they would be interested in referring their male partner to participate in an interview about partner self-testing and PrEP use during pregnancy. Only women whose partners know about their participation in the RCT will be eligible for study participation. Interested women will be provided a “study clinic referral form” to give their partners (Male Partner IDI Post RCT Referral Form). Once partners come for enrollment, they will be given more information on the study. It will be emphasized that participation is completely voluntary. If interested in participation, they will undergo the informed consent process.

Community Leader IDI: Community leaders will be identified during project initiation through consultations with facility staff and facility based community units. Facility staff or community health volunteers will provide community leaders with the referral letter inviting them to participate in the IDI. If community leaders contact study staff about participating in the IDIs, they will undergo the informed consent process.

Provider Focus Group Discussion (FGD): We will request providers working in MCH to participate in a FGD. These providers will be identified and recruited from serval study facilities. The FGD will focus on the provider experience with the study protocols, knowledge and attitudes regarding PrEP administration and counseling. Those who are willing and able to participate will undergo the informed consent process.

e) DATA COLLECTION PROCEDURES

All In-depth interviews and Focus Group Discussions (FGD) will be performed in a private area. Participants will meet a trained interviewer or moderator who will ask questions and take notes. Consent will be obtained from participants to take notes and audio record the discussion. The interviewer/moderator will describe procedures and norms for discussion and participation.

Participants will be given a chance to ask questions regarding procedures prior to the discussion. The socio-demographic information will be documented on separate forms. Socio-demographic information for the in-depth interviews of study participants and their male partners will include: age, marital status, education level, employment, number of children, and partner HIV status as shown in the participant survey portion of the in-depth interview guide. For Community Leaders and health care providers, socio-demographic information that will be captured includes age, education level, employment, roll in the community as show in the community leader in-depth interview guide.

Interviews with women will focus on understanding how and why women make decisions to accept and adhere to PrEP and the feasibility of different PrEP use strategies. We will conduct focus group discussions with healthcare workers from 4 study sites (2 per arm) who are involved in offering PrEP to understand logistical factors influencing healthcare worker ability and willingness to provide PrEP. All focus group discussions and interviews will be recorded and transcribed verbatim. To gain generalizability of barriers and facilitators influencing PrEP use, structured questionnaires will be administered to 30 randomly selected women per site at study exit. Questionnaires will be informed by themes emerging from the qualitative data.

Discussions will be guided by the interviewer or moderator using a discussion guide (attached). Prior to FGD, the interviewer will stress the importance of maintaining confidentiality within the group. Participants will receive unique identification numbers and will not be addressed by their real names so as to maintain confidentiality. Topics that generate the most discussion, participant attitudes, non-verbal gestures, and interaction dynamics among group members will be documented by the moderators. Discussions will be conducted in English, Kiswahili, or Luo depending on participant preferences. Thereafter, notes will be compared to audio-recordings to fill in missing information and transcribed to English (if necessary). Transcribed data will be de-identified. Tape-recorded discussions will be destroyed no later than 6 years after conducting the FGD or IDI.

Participants will be provided refreshments and Ksh. 500 to compensate for time and transportation expenses to participate in the study. We will provide this monetary compensation to each participant at the conclusion of each discussion.

f) DATA COLLECTION INSTRUMENTS

In-Depth Interview Guide for PrEP acceptance
In-Depth Interview Guide for PrEP adherence
In-Depth Interview Guide for Male Partners
Focus Group Discussion Guide
Exit Interview Questionnaire—This instrument will be developed following the In-Depth Interviews and focus Group Discussions.

g) TRAINING PROCEDURES

Dr. Gabrielle O'Malley will supervise training of facilitators for the qualitative components of this study. Dr. John Kinuthia will oversee training of staff on the exit interview survey and procedures.

11) STUDY MATERIALS:

Equipment: The grant award includes support to purchase 20 tablets, 4 audio recorders for qualitative studies, field office supplies (stationary, paper, toner), 4 desktop computers, clinic supplies to collect and store biological samples.

Personnel: The grant award includes support for UW, UNC, and KNH investigators, clinic personnel, the data team, and a study coordinator. Study personnel working in Kenya will be hired through KNH according to standard procedures.

12) DATA MANAGEMENT AND SECURITY

Overall Data management systems

Clinical and baseline data collected during the course of this study will be collected electronically via ODK data collection software. Data will be uploaded daily via ODK Survey from Android phones to the ODK Aggregate web server. Data will be transported via secure socket layer (SSL) and only accessible by authenticated users. Weekly reports will be generated to monitor study progress and troubleshoot problems. All computers, tablets (used for primary data collection), and individual study databases will be encrypted and password protected. Participants will be assigned a non-identifiable study code upon enrollment. Study analysts will receive only coded data. The links to patient identifiers will be retained in a password protected file on an encrypted computer.

External Advisory Panel

Prior to RCT initiation, we will convene an EAP to review study aims, statistical analysis plan, and protocol. At annual EAP meetings enrollment, retention, and pooled outcomes will be reviewed. Because of the short RCT timeline and potentially imbalanced follow-up time between sites, we do not plan to conduct an interim comparison of outcomes.

Data Ownership

The proposed project is a collaborative effort between investigators at the UW, UNC, and KNH. The aforementioned institutions will jointly share ownership of the data. Study investigators at the UW, UNC, and KNH will have full access to the data. Authorship on publications, conference presentations, abstracts and other materials generated from this study will reflect contribution to design, execution and analysis of the study.

Data Release/Sharing Policy

All data collected as part of this proposed research project will be made available without cost after registration to access or download files on a study related website (URL to be determined) and agreement to the data sharing agreement after completion of primary study analyses. The data sharing agreement will ensure commitments to:

1. Using the data only for research purposes and without attempting to identify study participants (if applicable);
2. Securing the data using appropriate computer technology;
3. Destroying or returning the data after analyses are completed;
4. Restrictions on redistribution of the data to third parties; and
5. Proper acknowledgement of the data resource.

13) STUDY LIMITATIONS AND HOW TO MINIMIZE THEM:

There may not be an HIV incidence difference between RCT arms. To address this, we outlined RCT benefits for varied trial outcomes in Table 4 above. As a programmatic RCT, characterization of some outcomes will be limited; the design was intentional to optimize program/policy relevance. We will combine MCH data abstraction with interviews and exams to address this as possible.

14) HUMAN SUBJECTS

Ethical Approval

We will obtain ethical approval from the University of Washington (UW) Human Subjects Division (IRB) and the Kenyatta National Hospital-University of Nairobi Ethics and Research committee (ERC).

Collaborating sites

The study will be conducted in collaboration with the UW, KNH, KEMRI, and CDC. The study will be reviewed by the KNH ERC and UW IRB and will not be started before approvals are obtained from all two organizational review boards. For this specific study, University of Washington investigators will not be directly involved in fieldwork, data collection, or study recruitment or consenting processes. Data analysis performed by investigators, co-investigators and personnel will be performed using only de-identified data.

15) LIST OF APPENDICES/ATTACHMENTS

I) DRAFT STATISTICAL ANALYSIS PLAN
II) CONSENT FORMS
III) GRANT APPLICATION
IV) FGD & IDI GUIDES
V) STANDARD OPERATING PROCEDURE FOR DBS

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