PrEPARE: PrEP in pregnancy, accelerating reach and efficiency

Study Protocol:
Principal Investigators: Grace John-Stewart, Pamela Kohler, Anjuli Wagner, John Kinuthia
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1) TITLE:

PrEPARE: PrEP in pregnancy, accelerating reach and efficiency

2) INVESTIGATORS (Roles and responsibilities):

Grace John-Stewart, MD, PhD (MULTIPLE PRINCIPAL INVESTIGATOR, Mentor K01)
(Responsible for overseeing all aspects of the project, including study design, administration (overseeing budget management and assuring regulatory requirements are met), leadership of staff, conduct of the study, analyses and interpretation of results.)
Professor
Departments of Global Health, Medicine, Epidemiology and Pediatrics, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359909, Seattle, WA 98104
Tel: +1-206-543-4278
Fax: +1-206-543-4818
Email: gjohn@uw.edu

Pamela Kohler, BSN, MPH, PhD (MULTIPLE PRINCIPAL INVESTIGATOR)
(Responsible for overseeing all aspects of the project, including study design, administration (overseeing budget management and assuring regulatory requirements are met), leadership of staff, conduct of the study, analyses and interpretation of results.)
Associate Professor
Department of Psychosocial & Community Health, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359932, Seattle, WA 98104
Tel: +1-206-616-7962
Email: pkohler2@uw.edu

Anjuli Wagner, PhD, MPH (MULTIPLE PRINCIPAL INVESTIGATOR)
(Responsible for overseeing all aspects of the project, including study design, administration (overseeing budget management and assuring regulatory requirements are met), leadership of staff, conduct of the study, analyses and interpretation of results.)
Acting Assistant Professor
Department of Global Health, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359909, Seattle, WA 98104
Tel: +1-978-460-2331
Email: anjuliw@uw.edu

John Kinuthia, MBChB, MMed, MPH (SITE PRINCIPAL INVESTIGATOR)
(Responsible for providing leadership on the study design and analyses and will oversee the study team in Kenya.)
Head, Department of Research & Programs, Kenyatta National Hospital
PO Box 20723-00202, Nairobi, Kenya
Tel: +254 0722 799-052
Email: kinuthia@uw.edu

Jared Baeten, MD, PhD (Mentor K01)
(Responsible for oversight and science for PrEP components)
Professor, Vice Chair
Departments of Global Health, Medicine, and Epidemiology, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359927, Seattle, WA 98104
Tel: +1-206-520-3808
Fax: +1-206-520-3831
Email: jbaeten@uw.edu

Bryan Weiner, PhD (Mentor K01)
(Responsible for providing methodologic leadership on implementation science)
Professor
Departments of Health Services and Global Health
University of Washington, Box 357965, Seattle WA, 98104
Tel: +1 206-282-7882
Email: bjweiner@uw.edu

Kristin Beima-Sofie, PhD (Co-Investigator)
(Responsible for providing methodologic leadership in qualitative methods)
Acting Assistant Professor
Department of Global Health
Department of Global Health, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359909, Seattle, WA 98104
Tel: +1-206-221-4970
Email: beimak@uw.edu

Ruanne Barnabas, DPhil, MD (Mentor K01)
(Responsible for providing methodologic leadership in budget impact analysis)
Associate Professor
Departments of Global Health, Allergy and Infectious Diseases, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359927, Seattle, WA 98104
Tel: +1-206-520-3813
Fax: +1-206-520-3831
Email: rbarnaba@uw.edu

Kenny Sherr, PhD, MPH (Mentor K01)
(Responsible for methodologic guidance on implementation science and quasi-experimental designs)
Professor
Departments of Global Health, Industrial Engineering, and Epidemiology
1107 NE 45th Street, Suite 350, Seattle, WA 98105
Tel: +1 206-221-7635
Email: ksherr@uw.edu

Peter Cherutich, PhD, MBChB, MPH (Mentor K01)
(Responsible for guidance in engaging policymakers in best practices development and implementation science research)
Senior Deputy Director of Medical Services
Ministry of Health
Tel: +254721924030
Email: pcheru2013@gmail.com

Jillian Pintye, PhD (Co-Investigator)
(Responsible for providing guidance on PrEP optimization strategy development and implementation)
Acting Assistant Professor
Departments of Global Health, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359927, Seattle, WA 98104
Tel: +1-206-520-3808
Fax: +1-206-520-3831
Email: jpintye@uw.edu

Julia Dettinger, MPH (RESEARCH SCIENTIST)
(Responsible for overseeing study coordination, ERC/IRB communication, protocol development and analysis)
Department of Global Health and Nursing, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359931, Seattle, WA 98104
Tel: +1-206-221-1041
Fax: +1-206-744-3693
Email: jcdettin@uw.edu

Laurén Gómez (STUDY COORDINATOR)
(Responsible for study coordination, ERC/IRB communication, protocol development and analysis)
Department of Global Health and Nursing, University of Washington
Harborview Medical Center, 325 Ninth Ave., Box 359931, Seattle, WA 98104
Tel: +1-206-685-5044
Fax: +1-206-744-3693
Email: gomezl4@uw.edu

3) COLLABORATING INSTITUTIONS

Kenyatta National Hospital, Nairobi, Kenya

4) FUNDING AGENCY

Funding type: Grant
Name of Funding agency: National Institutes of Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH)
Principal Investigator on Proposal: Grace John-Stewart, Jared Baeten
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Name of Funding agency: The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH)
Principal Investigator on Proposal: Grace John-Stewart, Pamela Kohler
Proposal Identification Number: R01 HD094630
Title of Proposal: PrEP Adherence Among AGYW: A Multidimensional Evaluation
Dates: 07/01/2017 - 06/30/2020

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Name of Funding agency: The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH)
Principal Investigator on Proposal: Grace John-Stewart, Pamela Kohler
Proposal Identification Number: R01 HD094630-03S1
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Funding type: Grant
Name of Funding agency: National Institutes of Mental Health (NIMH), National Institutes of Health (NIH)
Principal Investigator on Proposal: Anjuli Wagner
Proposal Identification Number: K01MH121124
Title of Proposal: Testing implementation strategies to improve delivery f PrEP for pregnant and postpartum women in Kenya
Dates: 08/06/2019 – 07/31/2024

5) SIGNATURES:

Grace John-Stewart, MD, PhD
Email: gjohn@uw.edu

Pamela Kohler, BSN, MPH, PhD
Email: pkohler2@uw.edu

Anjuli Wagner, PhD, MPH
Email: anjuliw@uw.edu

John Kinuthia, MBChB, MMed, MPH
Email: kinuthia@uw.edu

Jared Baeten, MD, PhD
Email: jbaeten@uw.edu

Bryan Weiner, PhD
Email: bjweiner@uw.edu

Kristin Beima-Sofie, PhD
Email: beimak@uw.edu

Ruanne Barnabas, DPhil, MD
Email: rbarnaba@uw.edu

Kenny Sherr, PhD, MPH
Email: ksherr@uw.edu

Peter Cherutich, PhD, MBChB, MPH
Email: pcheru2013@gmail.com

Jillian Pintye, PhD
Email: jpintye@uw.edu

Julia Dettinger, MPH
Email: jcdettin@uw.edu

Laurén Gómez

Email: gomezl4@uw.edu

6) Executive Summary

Title:	PrEPARE: PrEP in pregnancy, accelerating reach and efficiency
Objective:	Improve integrated delivery of PrEP to women seeking health services in maternal and child health and family planning clinics and translate implementation improvements into useful tools for policymakers and stakeholders
Aims:	1: To identify determinants of PrEP implementation and identify innovative and promising implementation strategies to increase fidelity (accuracy), penetration (screening), and integration of PrEP into MCH and FP clinics using a mixed methods approach. 2: To pilot and evaluate four strategies or bundles of strategies for optimized PrEP delivery for impact on penetration (screening), fidelity (accuracy), timeliness, efficiency, client and HCW satisfaction (including time), client PrEP knowledge, PrEP continuation, and PrEP adherence. We will test three strategies identified by stakeholders and 1 pre-developed package of strategies (video counseling, HIVST, and optimized delivery). 3: To review evidence, and understanding of study findings by stakeholders through stakeholder workshops, IDIs and surveys.
Methods	1: Qualitative focus group discussions and in-depth interviews, quantitative surveys 2: Interrupted time series quasi-experimental tests with surveys, record abstraction, and direct observation 3: Qualitative in-depth interviews and facilitated workshops
Population:	1: Health care workers, facility in-charges, PrEP users, PrEP policymakers and implementers 2: Health care workers, women seeking health services at family planning, maternal and child health, or PrEP care 3: PrEP policymakers, implementers, frontline HCW, PrEP ambassadors, community advisory board members
Sites:	Clinics in Kisumu County, Siaya County, and Homa Bay County, Kenya
Study Duration:	5 years

7) BACKGROUND

Women have persistent risk for acquiring HIV during pregnancy and the postpartum period. In settings with high HIV prevalence, HIV-uninfected women continue to be at risk for HIV acquisition during pregnancy and the postpartum period. In a systematic review, pooled HIV incidence during pregnancy was 4.7 per 100 person-years, comparable to incidence in 'high risk' groups [1]. Importantly, HIV incidence estimates in pregnant cohorts were derived from the general pregnant population, suggesting that the subset of pregnant women with partners who are HIV-infected or of unknown HIV status may have even higher HIV incidence. Both biologic and behavioral factors likely contribute to increased incidence during pregnancy and postpartum [2]. A recent analysis among HIV-uninfected women in serodiscordant partnerships demonstrated a 2.82-fold increased risk of HIV per-coital event during late pregnancy and a 3.97-fold increased risk during the postpartum period compared to non-pregnant/non-postpartum periods [2] (Figure 1).

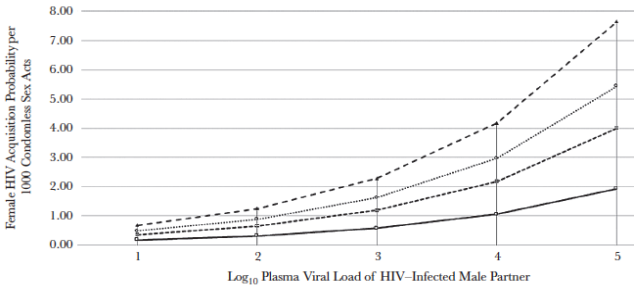

Figure 1. HIV risk in women increased in pregnancy and postpartum *Thomson, J Infect Dis Infect Dis*

To reach EMTCT targets, primary maternal HIV prevention is necessary. Prevention of mother-to-child HIV transmission (PMTCT) programs have yielded remarkable success in decreasing infant infections. Globally, WHO 2017 estimated 81% ART coverage among pregnant women in Africa [3]. Over the past decade, as population HIV testing has increased, the majority of HIV-infected women presenting to antenatal care (ANC) already know their HIV status—others are newly diagnosed at their first ANC visit. In well-functioning PMTCT programs, prompt maternal HIV diagnosis and ART can decrease MTCT risk to <1% [4]. As women with chronic HIV infection are effectively treated in PMTCT programs, new maternal HIV infections acquired during pregnancy and postpartum contribute an increasing proportion of infant HIV infections [5–7] (Figure 2). PrEP implementation for at-risk HIV-uninfected women in MCH clinics is necessary to protect women and to achieve elimination of mother-to-child HIV transmission (EMTCT) targets.

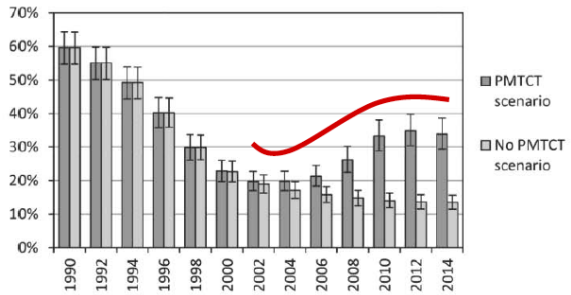

Figure 2. Percentage of MTCT from mothers infected after their first ANC visit *Johnson, JAIDS 2012*

Oral pre-exposure prophylaxis (PrEP) is a female-controlled, acceptable, effective HIV prevention evidence-based intervention [8–10] **and is recommended during pregnancy in high incidence settings**. WHO recommendations note that current safety data [11–14] support the provision of PrEP for individuals at substantial risk [15]. Kenyan national guidelines support provision of PrEP during pregnancy [16]. Pregnant women report finding PrEP acceptable and desirable for HIV prevention [17]. PrEP can protect pregnant women who do not know their partner's HIV status and cannot negotiate condom use. While condoms and partner antiretroviral treatment (ART) are effective HIV prevention methods, they are not feasible for many women [18]. Pregnant women are often unaware of their male partner's HIV status and fear broaching the discussion, particularly in relationships with intimate partner violence [19]. In a study from Western Kenya, only 33.6% of pregnant women reported knowing their partner's HIV status [20]. While couples testing is encouraged in antenatal care, uptake remains low [21,22]. Women in regions with high HIV prevalence with partners who are HIV-infected or who have unknown HIV status are at risk for HIV. In addition, women whose partners are HIV-uninfected may suspect or know that their partners have external partnerships, or women may be in polygamous marriages, and may fear that a currently HIV-uninfected partner will acquire HIV. Women are often unable to negotiate condom use, particularly in married or longstanding partnerships [20], and this inability is exacerbated during pregnancy.

Two large projects in Kenya have implemented PrEP for peripartum women: an ongoing cluster randomized trial, *PrEP Implementation for Mothers in Antenatal Care (PrIMA)* (NIAID R01: MPI John-Stewart, Baeten) and

a recently completed implementation project, *PrEP Implementation for Young Women and Adolescents (PrIYA)* (PEPFAR: MPI John-Stewart, Baeten). The PrIMA and PrIYA projects have integrated PrEP delivery into routine antenatal care (ANC) clinics in the Kenyan public health sector. The PrIYA project took place in 16 facilities and screened >10,000 women and initiated ~4,100 on PrEP and is the first and largest implementation project for PrEP delivery during pregnancy in the world. The ongoing PrIMA trial takes place in 20 facilities and will enroll and offer PrEP to ~4,000 pregnant women. This study will leverage the research infrastructure, political will, and unique implementation experience from the ongoing PrIMA and past PrIYA projects.

Delivering PrEP in MCH clinics is a 'one-stop' approach to protect pregnant and postpartum women. We recently demonstrated that it is feasible to deliver PrEP in MCH clinics in a program supported by a DREAMS-Innovation Challenge. The *PrIYA* program incorporated PrEP provision in MCH clinics piloted by a full-time extra nurse in 16 facilities in Kisumu County, Kenya and additionally trained personnel at 21 'mentored' clinics to implement PrEP within MCH or FP services [23]. Importantly, women and health care workers (HCW) felt it was critical to provide PrEP at the MCH or FP clinic rather than refer women to HIV treatment Comprehensive Care Centers (CCC) to minimize stigma and decrease time spent by women as they shuttled between programs.

PrEP integration in MCH clinics needs to avoid overburdening the health system and HCW. The PrIYA program aimed to provide proof of concept that PrEP delivery in MCH was acceptable to pregnant women and feasible operationally. We designed the program to circumvent known health systems challenges by providing full-time nurses to work with each clinic to build a PrEP delivery system within the MCH clinic. While the PrIYA implementation project added staff to clinics, scaling up PrEP delivery through MCH clinics will require health systems innovations that do not require increases in human resources. MCH clinics provide routine antenatal care (ANC) to pregnant women and postnatal care (PNC) to mothers and children. The primary mandate for MCH services is to provide high quality maternal and child health care and to improve maternal and child survival. Thus, the MCH clinic is tasked with monitoring pregnancy, syphilis and hemoglobin testing, malaria prophylaxis, and PMTCT interventions. Nurses need to have multi-faceted training to be vigilant for pregnancy complications and child morbidity, while providing routinized services such as PMTCT.

Systems to decrease workload for nurses, including task-shifting for PMTCT and PrEP, are important to decrease HCW burden on MCH care [24–26]. Regional evaluations of MCH clinics have noted uneven quality of care, need for improved training to systematically recognize pregnancy danger signals, and monitor children [27,28]. In addition, PMTCT programs need persistent oversight to maintain gains or to address recent declines in performance. Within PTMCT programs, HIV testing coverage, ART provision, retention and early infant diagnosis all have room for improvement and innovation. Adding PrEP to MCH clinics must not detract from vital routine MCH services. A streamlined approach that integrates with PMTCT services and minimizes HCW workload and optimizes client experience is needed.

8) LITERATURE REVIEW

Implementation science to accelerate scale up of scientific discoveries: While discovery science was crucial in determining PrEP efficacy and effectiveness, scaling up PrEP for pregnant women will require implementation science [29]. Implementation science is the systematic approach of identifying strategies to scale up evidence-based interventions and promote their widespread application in routine practice. Implementation science includes the identification of determinants of poor or strong implementation and then tests implementation strategies to overcome specific barriers and improve implementation outcomes. Implementation strategies can address individual, collective, or structural-level changes [30]; a review of implementation strategies has been compiled, ranging from altering incentive structures, to using audit and feedback, to modifying job responsibilities [31]. Implementation strategies can be introduced individually or packaged to address a series of determinants.

There have been no implementation strategies tested to improve PrEP delivery during the peripartum period in resource-limited settings.

Models of integrating PrEP delivery into antenatal care: Between June 2017 and December 2018, women of reproductive age seeking MCH and FP services at 16 clinics were screened for behavioral risk factors and offered PrEP in accordance with Kenyan national PrEP guidelines (developed in May 2017). Time-and-motion data were collected to estimate time required during PrEP integration into MCH and FP clinics [23]. Nurses worked with MCH and FP clinic teams to develop optimal systems for incorporating PrEP into existing clinical flow and procedures. These discussions led to two models, the integrated (or "co-delivery") approach and the sequential approach, which depended on clinic configuration, staffing and flow [23] (Figure 3). We found that implementing PrEP in MCH required a median of 18 additional minutes per client that initiated PrEP, and 13 additional minutes per client that did not initiate PrEP [23]. While the time-cost was modest for a single client, this one-on-one approach cumulatively increases MCH workload; 20 clients at ~10-15 minutes per client would add 5 hours of HCW labor per day.

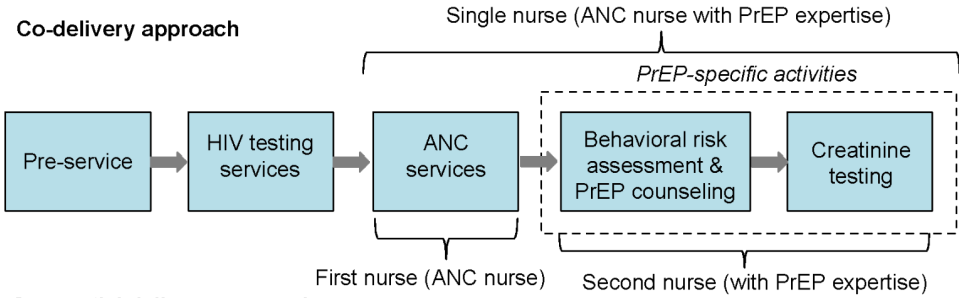

Figure 3: Models of PrEP integration in ANC

Screening and uptake are heterogeneous: Barriers to integrating PrEP delivery into ANC are not well characterized due to limited implementation experience globally. Integrating PrEP services into ANC includes adding steps to a typical ANC visit, including repeat HIV testing, behavioral risk assessment, creatinine testing, PrEP counseling, and PrEP dispensing. These steps add additional workload with fixed numbers of health workers, increasing both waiting and service delivery time. There was substantial heterogeneity between clinics in the penetration of PrEP screening (*the proportion of women who are screened for PrEP / total women receiving antenatal or postnatal services*), limiting uptake of subsequent steps (Figure 4). The large number of health workers and heterogeneous clinics who have implemented PrEP during the peripartum period provides an excellent learning opportunity to identify further determinants of poor and of successful implementation. Effective implementation strategies are needed to increase coverage of PrEP provision in ANC, while addressing systems-level and organizational barriers.

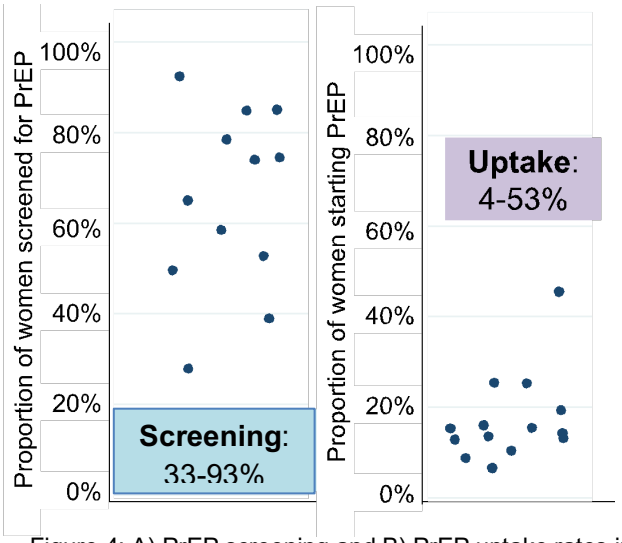

Figure 4: A) PrEP screening and B) PrEP uptake rates in PrIYA sites

Video based counselling approaches:

Table 1: Benefits and drawbacks of video

	Barriers overcome by video
Data available	Heterogeneous PrEP coverage due to high patient volumes - Saves HCW time or enables education without HCW time [35] Unavailability of counselors after hours [32] - Allows for all hours counseling Language barrier - Can be translated into different languages [32,35–37]

	Inconsistent information given by counselors - Consistent messages result in higher knowledge scores [34–36,38,39,41] Client fear of asking sensitive questions - Opportunity to learn and review sections with no embarrassment [42]
Pending questions	Unclear whether benefits shown in high resource settings translate to resource-limited settings Unclear whether nuanced decision-making information inherent in PrEP counseling lends itself well to standardized video format

There are many potential implementation strategies that may improve PrEP delivery in MCH and FP clinics. Video-based education provides standardized messages, can be engaging, and saves time for women and HCW. Integrating PrEP into MCH clinics requires that women receive education regarding PrEP, confirmation of HIV-uninfected status and medical eligibility, and advice regarding PrEP adherence. Video-based education has been used in HIV pre-test and post-test counseling to achieve both high testing coverage and high HIV-related knowledge, allowing for standardized messaging in multiple languages, available at all hours [32–37]. Compared to counselor-delivered education, video-based education is easier to update, scale, and standardize. Video-based education could provide standardized messaging regarding HIV risk in pregnancy/postpartum, benefits/risks of PrEP, and importance of adherence and serial HIV testing. Women could listen to video-based educational content while waiting for their routine MCH appointment (typically a 90-minute wait). This process would decrease nurse time with women and allow women to request PrEP based on the video and ask further questions, if needed. Video-based education has been shown to be as effective as in-person counseling [32,34,37–40].

Other strategies for PrEP optimization

Serial HIV testing for PrEP can be expedited by HIV self-testing in clinics. HIV retesting is required for all clients on PrEP, but the high volume of testing may overburden fixed numbers of HCW, or may shift HCW away from other tasks. Rapid oral HIV self-testing (HIVST), which is saliva-based, has excellent diagnostic performance, with high sensitivity and specificity when compared to standard rapid blood HIV testing [43,44]. HIVST has been used in varied settings and recently been expanded by the Kenya Ministry of Health as an option to increase HIV testing in Kenya. A recent cluster randomized trial in Malawi demonstrated that facility-based HIVST in outpatient waiting areas significantly increased number and proportion of clients tested [45,46]. HIVST for retesting for PrEP users is being tested among serodiscordant couples in Kenya, and is anticipated to increase fidelity (accuracy in adherence) to retesting guidelines, save HCW time, and be more cost-effective.

Policy Implications

Policymakers may consider affordability data, in addition to effectiveness data, to make relevant, local PrEP policy decisions. Cost-effectiveness analyses are useful for comparing interventions against one another; however, interventions considered “cost-effective” by standard Gross Domestic Product thresholds may not be affordable, particularly in resource-limited settings [47,48]. A recent review of PrEP cost-effectiveness called for budget impact analyses to assess affordability [49]. Budget impact analyses quantify total cost when implemented on a large scale, which helps policymakers determine whether a specific intervention is affordable given budget constraints. As Kenya moves towards adopting universal health care this year, this type of analysis will be particularly needed. PrEP is a relatively expensive evidence-based intervention; the Ministry of Health has outlined a series of PrEP cost research questions, including drivers of total cost and cost of delivery through varied service delivery platforms, to direct their roll out of PrEP nationally. Gaps exist in understanding how policymakers use research to make decisions. Systematic reviews have revealed a weak understanding in how policymakers consider scientific evidence in making policy decisions [50]. This study will explicitly address this gap, providing innovative data to promote more rapid translation of research findings into policy.

9) GUIDING FRAMEWORKS

Overview: This study uses a series of 3 frameworks to inform the study design and data collection elements. Traditional psychosocial or behavioral theory models are widely used to inform public health research, reflecting mechanisms at the individual, group, and societal levels. These theories are essential in selecting appropriate interventions, elucidating mechanisms of action, and understanding barriers at multiple levels. However, investigating implementation requires that these traditional theories be adapted or modified to reflect distinct needs of implementation science. The three frameworks or theories described below have been derived from traditional psychosocial or behavioral models and specifically modified to reflect such implementation science needs. They have been applied to this study to select study outcomes, inform data collection tools, and integrate information from different aims.

Aim 1: In-Depth Interviews and Focus Group Discussions

CFIR Model: We will utilize the Consolidated Framework for Implementation Research (CFIR) to inform Aim 1 (*Figure 5).* The CFIR is an original framework for implementation science that synthesizes 20 unique frameworks into a single consolidated framework that describes determinants in terms of 5 major domains (intervention characteristics, outer setting, inner setting, characteristics of individuals, and process) and 39 constructs within those domains [53]. CFIR is flexible and can serve both as an explanatory and predictive framework. We will use CFIR first as an explanatory framework in Aim 1 to identify factors that served as positive and negative determinants (barriers and facilitators) to PrEP integration into ANC, and to understand why the wide range of implementation strategies tried in PrIYA and PrIMA had different implementation success. Subsequently, we will use CFIR as a predictive framework to hypothesize which implementation strategies might overcome specific barriers to inform Aim 2. During the interviews with policymakers, we will use the CFIR to create question guides; the goal of these interviews will be to understand which of the CFIR constructs are considered by policymakers, and to understand how they consider cost data in decision-making.

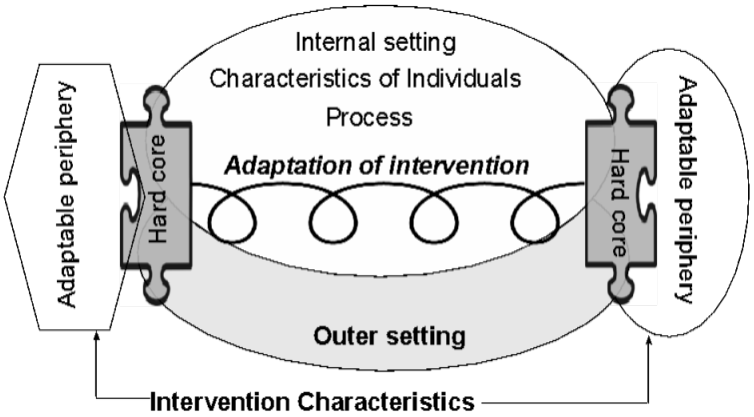

Figure 5: Consolidated Framework for Implementation Research

Aim 2: Interrupted Time Series Intervention testing

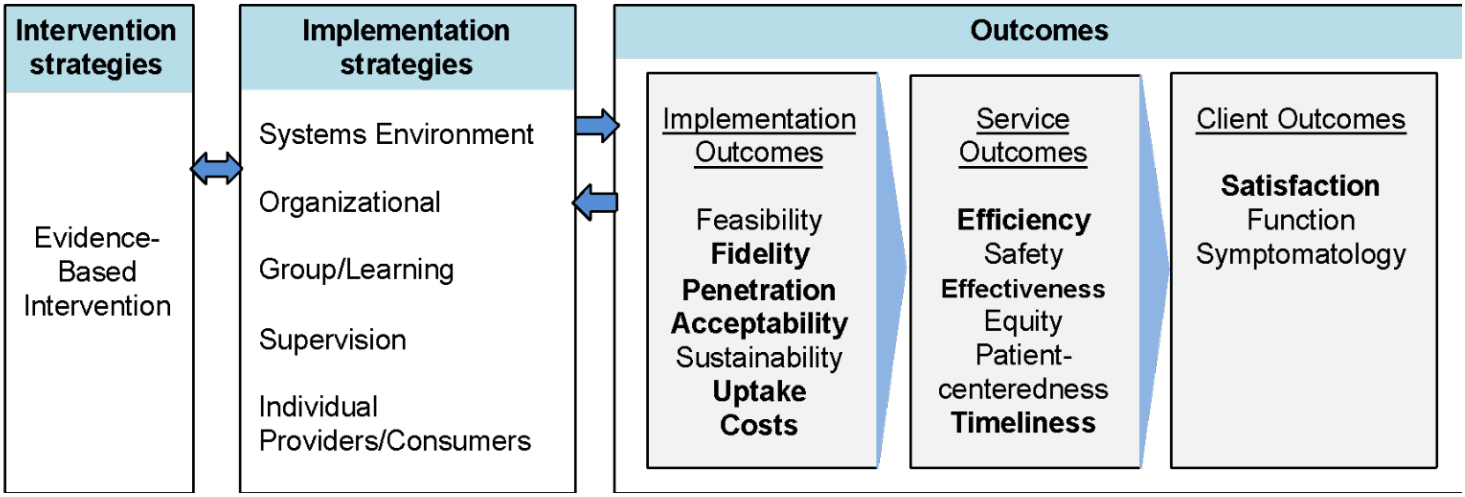

Figure 6: Adapted Proctor model of taxonomy of outcomes in health research

Proctor Model: A review in 2000 noted that it took, on average, 17 years for just 14% of effective evidence-based interventions to become part of routine clinical practice [51]. While discovery science has tended to dominate HIV research historically, there is a growing recognition of the need for implementation science to bring promising

evidence-based interventions to scale to realize their full impact. Implementation science is a new scientific field; while terminology and definitions are evolving, this application will use NIH terminology and define terminology that is unique to implementation science. The Proctor model characterizes 1) implementation outcomes, 2) service, and 3) client outcomes, noting that implementation strategies are applied to improve implementation of interventions from discovery science [52] (Figure 6). This study will measure: 1) implementation outcomes, including fidelity *(proportion of women who receive all PrEP specific steps in a visit: HIV testing, HIV risk screening, PrEP counseling*), penetration (*proportion of women who are screened for PrEP / total women receiving antenatal or postnatal services*), acceptability, uptake, and costs; 2) service outcomes, including efficiency, effectiveness, and timeliness, and 3) client outcomes, including satisfaction. Operational definitions of each outcome are provided in Section *11.3.9 Variables*.

Summarizing study results across aims

PRISM framework: We will use the PRISM (Practical, Robust Implementation and Sustainability Model) Model, which synthesizes the RE-AIM framework, Model for Improvement, and the Chronic Care model. This implementation science model is particularly well-suited to scaling up new interventions, optimizing performance, and considering sustainability [54]. It considers implementation science RE-AIM outcomes (reach, effectiveness, adoption, implementation, and maintenance) as a function of multiple levels of provider and patient perspectives of the intervention, characteristics of the recipient organization and patients, and infrastructure available for implementation and sustainability, as well as the external environment (Figure 7). Aim 1 will provide qualitative information about key stakeholder perspectives of MCH-PrEP and FP-PrEP integration, guided by the multiple levels of the social-ecological framework [55,56]. Aim 1 will further provide quantitative data about the organizational and health systems issues and factors related to environment, infrastructure, and facility organization. Aim 2 will pilot the optimized delivery model and measure implementation outcomes.

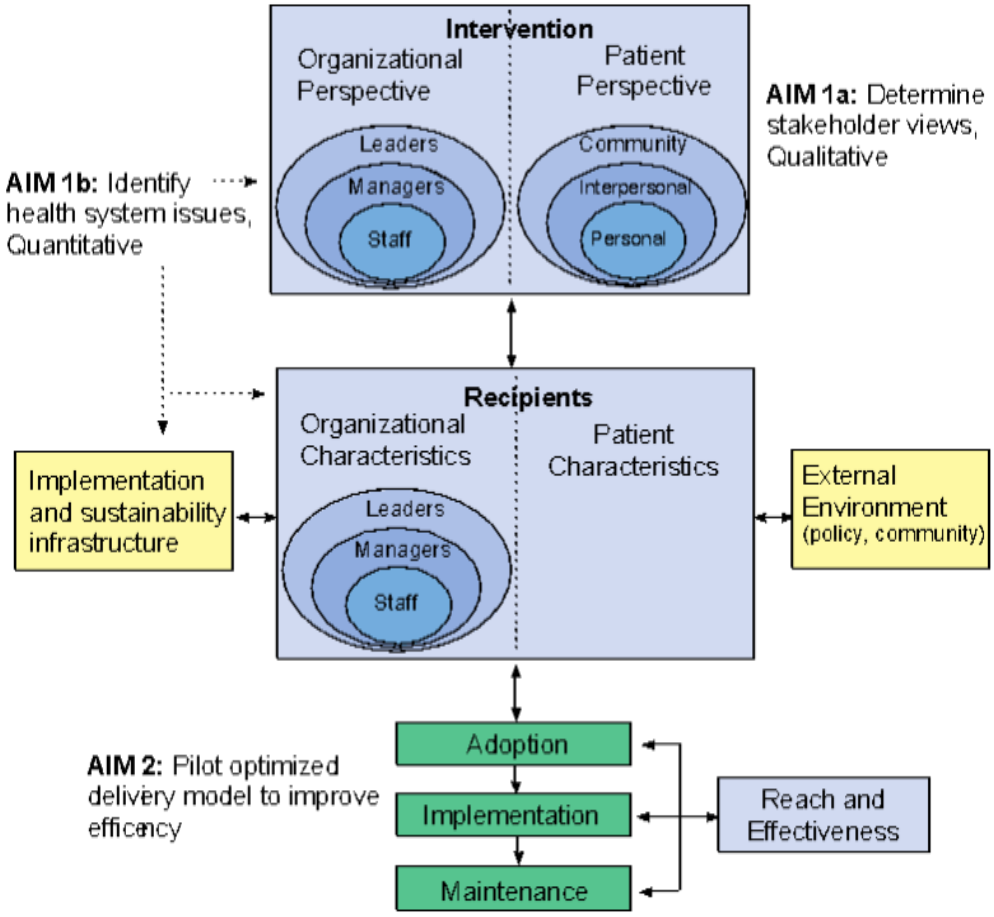

Figure 7: PRISM model with study aims mapped to components

10) RATIONALE

It is critical to optimize the delivery and integration of PrEP into existing health services for women in resource-limited settings. Applying robust implementation science methods to define barriers, test strategies, and engage with stakeholders to support dissemination are critical.

11) HYPOTHESIS, OBJECTIVES, & STUDY QUESTIONS:

AIM 1: To identify determinants of PrEP implementation and identify innovative and promising implementation strategies to increase fidelity, penetration, and integration of PrEP into MCH and FP clinics using a mixed methods approach.
Hypothesis 1: We predict that determinants will include overburdened staff, inefficient patient flow, insufficient provider knowledge in counselling techniques, and paperwork burden. We predict that promising implementation strategies may include HIV self testing, task shifting PrEP risk assessment, video-based PrEP counseling, and streamlining data collection registers.

AIM 2: To pilot and evaluate four strategies or bundles of strategies for optimized PrEP delivery for impact on penetration, fidelity, timeliness, efficiency, client and HCW satisfaction (including time), client PrEP knowledge, PrEP continuation, and PrEP adherence. We will test three strategies identified by stakeholders and 1 pre-developed package of strategies (video counseling, HIVST, and optimized delivery).
Hypothesis 2: We predict that several implementation strategies will be effective in improving implementation and service outcomes.

AIM 3: To review evidence, findings, and understanding of study findings through two stakeholder workshops and to evaluate these workshops through IDIs and surveys.
Hypothesis 3: We predict that meaningful stakeholder engagement will ensure that tested implementation strategy findings are more widely disseminatable.

12) STUDY DESIGN AND METHODOLOGY

12.1) STUDY AREA DESCRIPTION:

The proposed study will be conducted in twenty health care facilities in Kisumu, Siaya, and Homa Bay counties. Facilities will be selected for inclusion if they have ongoing PrEP delivery through maternal and child health (MCH) clinics and if they have ongoing PrIMA or PrIYA-SP activities. At least ten of the facilities selected for inclusion should have PrEP delivery occurring in Family Planning (FP) clinics in addition to MCH clinics.

Table 2: Summary of study aims, population, design, data collection, sample size, outcomes and inclusion

	Aim 1	**Aim 2**	**Aim 3**
	Implementation determinants, implementation strategies, and service availability	**Implementation strategy tests**	**Stakeholder views on research findings and best practices**
Population	Health care workers (HCW), Facility in-charges, PrEP users, PrEP policymakers	HCW, clients attending study clinics	PrEP policymakers, implementers, frontline HCW, PrEP ambassadors, community advisory board members
Design	Qualitative and quantitative cross-sectional design	Interrupted time series (ITS) quasi-experimental design	Qualitative cross-sectional design
Data collection	In-depth interviews (IDI), Focus Group Discussions (FGD), and quantitative surveys	Register abstraction of existing program data, client observation, quantitative surveys	IDI, facilitated workshops
Sample size	HCW: up to 26 FGDs with 7-10 participants each, and quantitative survey with 260 participants Facility in-charge: In-charges from	Register abstraction of existing program data: unable to predict total number of records to be abstracted; expected abstraction of	PrEP policymakers: up to 15 IDIs Workshop participants: up to 50 participants

	26 facilities PrEP users: up to 4 FGDs with 7-10 participants each PrEP policymakers and implementers: up to 40 participants for in-depth interviews	~200 clients per month per clinic Client observations: up to 200 clients per clinic per interrupted time series experiment cycle Quantitative surveys: up to 240 clients per clinic per interrupted time series experiment cycle; up to 20 HCW per clinic per interrupted time series experiment cycle	
Outcome(s) of interest	Implementation determinants, range of potential implementation strategies, prioritized implementation strategies, service availability and readiness	PrEP penetration, fidelity, uptake, continuation, adherence, efficiency, timeliness, client and HCW satisfaction, client PrEP knowledge, service availability	Decision-making process and understanding of budget impact analyses, consensus-determined best practices for PrEP delivery and integration
Inclusion criteria	HCW: work at a facility involved in study, involved in PrEP service delivery, ≥18 years Facility in-charge: work at a facility involved in study, ≥18 years PrEP users: female PrEP users at study facilities, ≥15 years (includes emancipated minors) PrEP policymakers and implementers: involved in making decisions related to PrEP at national or county level, ≥18 years	HCW: work at a facility involved in study, involved in PrEP service delivery, ≥18 years Clients: female clients seeking health services at study facilities, ≥15 years (includes emancipated minors)	PrEP policymakers and implementers: involved in making decisions related to PrEP at national or county level, ≥18 years Other stakeholders: stakeholder in in PrEP delivery, ≥18 years; adolescent PrEP ambassadors, ≥15 years
Exclusion criteria	N/A	N/A	N/A

12.2) AIM 1:
To identify determinants of PrEP implementation and identify innovative and promising implementation strategies to increase fidelity, penetration, and integration of PrEP into MCH and FP clinics using a mixed methods approach. Operational definitions of each outcome are provided in Section *11.3.9 Variables*.

	Aim 1
	Implementation determinants, implementation strategies, and service availability
Population	Health care workers (HCW), Facility in-charges, PrEP users, PrEP policymakers
Design	Qualitative and quantitative cross-sectional design
Data collection	In-depth interviews (IDI), Focus Group Discussions (FGD), and quantitative surveys
Sample size	HCW: up to 26 FGDs with 7-10 participants each, and quantitative survey with 260 participants Facility in-charge: In-charges from 26 facilities PrEP users: up to 4 FGDs with 7-10 participants each PrEP policymakers and implementers: up to 40 participants for in-depth interviews
Outcome(s) of interest	Implementation determinants, range of potential implementation strategies, prioritized implementation strategies, service availability and readiness
Inclusion criteria	HCW: work at a facility involved in study, involved in PrEP service delivery, ≥18 years Facility in-charge: work at a facility involved in study, ≥18 years PrEP users: female PrEP users at study facilities, ≥15 years (includes emancipated minors) PrEP policymakers and implementers: involved in making decisions related to PrEP at national or county level, ≥18 years
Exclusion criteria	N/A

12.2.1) STUDY DESIGN
Mixed methods including Focus Group Discussions (FGDs), In-Depth Interviews (IDI), Health Care Worker (HCW) surveys, and Service Availability and Readiness Assessment (SARA) with Facility In-Charges

12.2.2) STUDY POPULATIONS
Health Care Workers:
HCW working on 16 facilities will be approached for participation in 26 (16 MCH, 10 FP) clinic-based FGD and to complete a quantitative survey to understand their experience with PrEP delivery. Facility in-charges at all facilities from PrIMA and PrIYA will be identified and approached to conduct a health systems survey.

HCW Inclusion Criteria:
- HCW at a study facility in Kisumu, Homa Bay, or Siaya Counties.

PrEP users
Up to 40 PrEP users will be identified from participating facilities and invited to participate in FGDs to explore their experience with PrEP use. Ten participants from each of the following groups will be invited to an FGD.
- FP-based PrEP user, 15-24 years old
- FP-based PrEP user, 25 or older
- MCH-based PrEP user, 15-24 years old
- MCH-based PrEP user, 25 or older

PrEP user inclusion criteria:
- Female gender

- Receiving care in an MCH or FP clinics at a facility
- ≥15 years old
- Able and willing to provide informed consent for participation
- Currently using PrEP for any duration

PrEP Policy Makers and Implementers
Up to 40 policy makers and representatives from PrEP implementing partners will be identified and invited to participate in in depth interviews.

PrEP Policy Maker and Implementer Inclusion Criteria:
- Has a role at the National or County level in PrEP policy making or implementation
- Able and willing to provide informed consent

12.2.3) SAMPLE SIZE DETERMINATION AND FORMULAS USED
FGD sample size: We will conduct 26 FGDs with HCW and 4 FGDs with PrEP users. Each FGD will consist of 7-10 participants, sufficient to generate conversation without being too large to become intimidating [57,58]. We will aim to recruit health workers from varying cadres, including those involved in antenatal and postnatal care, HIV testing services, and laboratory. Based on previous studies in this region with health workers and PrEP users, we predict that our sample size will be sufficient to reach theoretical saturation, that no new themes are identified with each additional FGD [59].

IDI sample size. We will conduct 26 IDIs with facility in-charges and 40 IDIs with policymakers and implementers. Based on previous experience conducting qualitative research, we believe our sample size will be enough to reach sufficient diversity and data saturation [60,61].

Quantitative prioritization of strategies: We will aim to enroll up to 260 individuals. Given that these data are for prioritization purposes, rather than to identify determinants associated with high and low performance, formal power calculations were not appropriate. Instead, analysis will involve calculating *mean frequency, strength of influence, and likelihood of success scores,* accounting for unequal numbers per cluster by weighting observations.

12.2.4) RECRUITMENT PROCEDURES
Health Care Workers:
Study staff will communicate with county-level health officials of Kisumu, Homa Bay and Siaya Counties to compile a list of facilities that meet our eligibility criteria. Study staff will communicate the study purpose and objectives to in-charges of the facilities identified. Facility in-charges will be asked to introduce the facility's HCWs. A member of the study team will randomly select HCWs at each facility and contact each of them either in-person or by phone to invite them to participate in the FGD or survey. The study background and procedures will be explained to potential HCW participants to inform the HCWs' decision to participate. The HCWs will also be assured that participation in the FGD or survey will not impact their employment.

FGDs: All FGDs with HCWs will be conducted by qualitative study staff at the 16 K-PrOM facilities. Up to ten HCWs at each facility will be invited to participate in the FGD. A member of the study team will then schedule the FGD for HCWs willing to participate at a time convenient for the majority of the potential participants.

Facility In-Charge:
In addition to participating in the HCW FGDs, facility in-charges will be approached to complete a health systems survey.

PrEP Users:
During antenatal, early postnatal, and family planning care visits, study staff will approach women, request to review their health records card to determine whether they are currently taking PrEP, and will describe the

purpose of the FGDs and invite interested women to participate. Study staff will track the age of interested participants to ensure that no more than 10 AGYW and 10 older women participate in the FGDs at each facility.

PrEP Policy Makers and Implementers:
PrEP Policy Makers and Implementers will be identified through consultation with NASCOP and the PrEP Technical Working Group at NASCOP. We will invite identified policy makers to participate in the IDI.

12.2.5) ENROLLMENT & STUDY PROCEDURES

General procedures for all IDIs/FGDs
Consent will be obtained from participants to take notes and audio record all focus group discussions (FGDs). Trained study staff will be responsible for conducting informed consent procedures and enrolling participants. During enrollment, participants will be informed of the facilitation procedure, including the length (30-120 minutes each) and that the FGDs/IDIs will be audio recorded and transcribed. Participants scheduled to return at a later date for an IDI or FGD will provide contact information and names upon consent, for the purpose of reminding them of the interview date. Participants will meet a trained interviewer or moderator who will ask questions and take notes. All FGDs will be performed in a private areas by trained study staff members and in local languages, as needed.

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. After IDI/FGD completion, participants may re-contacted to verify the accuracy of the data collected. To compensate for time and travel costs, each participant will be offered 1000 Kenyan Shillings (KES) following completion of the IDI/FGD. Once the IDI/FGD is completed, transcripts of recordings will be stored without links to patient identifiers, except for those needed to link with consent forms, for up to six years.

We have included draft IDI and FGD guides in Appendix 2. Although the content of the interview and focus group guides will remain the same throughout the study, the phrasing and order of the questions are subject to change after pilot testing of these tools. If the content areas covered in the guides change, they will be resubmitted for IRB approval.

PrEP user FGDs:
Socio-demographic information for the PrEP user FGDs 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. FGDs with women will explore experiences with initiating and continuing PrEP with a focus on factors and actions impeding and/or contributing to optimal PrEP integration and implementation strategies that have been or could be employed to improve efficiency, synergy, and access.

HCW FGDs:
For HCW FGDs, sociodemographic information will include age, education level, duration of employment, and experience providing PrEP. The HCW FGD will use discussion guides based on Consolidated Framework for Implementation Research (CFIR) to elicit information about health worker experiences with specific implementation strategies and opinions on modifications to these strategies to further improve implementation outcomes of fidelity and penetration.

HCW Surveys:
HCW will be asked to complete a survey that captures the frequency and perceived strength of influence of each PrEP delivery determinant and the perceived likelihood of success of a variety of possible PrEP optimization strategies, all using 3 point Likert scales with semantic anchors (e.g. never, sometimes, frequently). HCWs will be asked about transitioning PrEP delivery from research (PrIMA & PrIYA-SP) staff to clinic staff. HCWs will also be asked about the impact of COVID-19 on PrEP delivery and clinic duties. The survey will include questions about their daily experiences, sociodemographic information such as age, education level, duration of

employment, and experience providing PrEP. Surveys will be administered in-person, over telephone or electronically via a computer-assisted self-interview. Participants will receive a reimbursement of 600 KES following completion of the survey. Mobile money transfer will be used for individuals participating remotely.

PrEP Policy Maker and Implementer IDI
For PrEP policy maker and implementer IDIs, sociodemographic information will include age, education level, duration of employment, and experience providing PrEP. PrEP policy maker and implementer IDI guides will also include knowledge, attitudes, and beliefs about PrEP delivery strategies, preferred and essential attributes for PrEP delivery best practices, and experiences with PrEP delivery at national, county, or partner organization level.

Planned Analyses:
PrEP user FGDs: We will use qualitative methods to explore women's experiences with initiating and continuing PrEP with a focus on factors and actions impeding and/or contributing to optimal PrEP integration.

HCW FGDs and Surveys: Survey data collected from HCWs will be analysed descriptively with *mean frequency, strength of influence, and likelihood of success scores,* accounting for unequal numbers per cluster by weighting observations, to identify HCW preferences in PrEP optimization strategies.

The HCW FGD will use the Consolidated Framework for Implementation Research (CFIR) to elicit information about health worker experiences with specific implementation strategies and opinions on modifications to these strategies to further improve implementation outcomes of fidelity and penetration.

PrEP Policy Maker and Implementer IDI: We will use qualitative methods to explore knowledge, attitudes, and beliefs about PrEP delivery strategies, preferred and essential attributes for PrEP delivery best practices, and experiences with PrEP delivery at national, county, or partner organization level.

12.2.6) LABORATORY METHODS
Not applicable

12.2.7) DATA COLLECTION INSTRUMENTS
- PrEP user focus group guide
- PrEP user demographic information
- HCW Survey
- HCW FGD guide
- Service Availability and Readiness Assessment Tool
- PrEP policy maker and implementer interview guide

12.2.8) VARIABLES: Outcomes, indicators, and source documents
Not applicable

12.2.9) TRAINING PROCEDURES
Drs. Beima-Sofie and Wagner will supervise training of facilitators for the qualitative components of the study.

Study Materials
- HCW FGD Consent Form
- HCW Survey Consent Form
- Policy Maker IDI Consent Form
- PrEP User FGD Consent Form

12.3 AIM 2:

To pilot and evaluate four strategies or bundles of strategies for optimized PrEP delivery for impact on penetration, fidelity, timeliness, efficiency, client and HCW satisfaction (including time), client PrEP knowledge, PrEP continuation, and PrEP adherence. We will test three strategies identified by stakeholders (based on qualitative information from Aim 1) and 1 pre-developed package of strategies (video counseling, HIVST, and optimized delivery). Operational definitions of each outcome are provided in Section *11.3.9 Variables*.

	Aim 2
	Implementation strategy tests
Population	HCW, clients attending study clinics
Design	Interrupted time series (ITS) quasi-experimental design
Data collection	Register abstraction of existing program data, client observation, quantitative surveys
Sample size	Register abstraction of existing program data: unable to predict total number of records to be abstracted; expected abstraction of ~200 clients per month per clinic
	Client observations: up to 200 clients per clinic per interrupted time series experiment cycle
	Quantitative surveys: up to 240 clients per clinic per interrupted time series experiment cycle; up to 20 HCW per clinic per interrupted time series experiment cycle
Outcome(s) of interest	PrEP penetration, fidelity, uptake, continuation, adherence, efficiency, timeliness, client and HCW satisfaction, client PrEP knowledge, service availability
Inclusion criteria	HCW: work at a facility involved in study, involved in PrEP service delivery, ≥18 years
	Clients: female clients seeking health services at study facilities, ≥15 years (includes emancipated minors)
Exclusion criteria	N/A

12.3.1) STUDY DESIGN

We will utilize interrupted-time series design; this is a quasi-experimental design that compares data before an intervention is introduced to data after the intervention is introduced, and controls for time trends (Figure 8). Four rounds of interrupted-time series evaluations to evaluate four PrEP optimization interventions, three identified by stakeholders based on qualitative information in Aim 1, and one pre-developed package of interventions (video-based PrEP counselling, HIV Self-Testing [HIVST], and optimized PrEP delivery). Each of the four rounds of interrupted-time series evaluations will include 4 facilities receiving the intervention and 4 facilities serving as an ongoing concurrent comparator group; these 4 facilities will not receive any of the packages of interventions, but will undergo the same data collection procedures. There will be three months of baseline data collection and a three month intervention period for each of the 4 intervention facilities, and six months of data collection during the same calendar period for each of the 4 comparator clinics for each of the 4 interrupted-time series interventions.

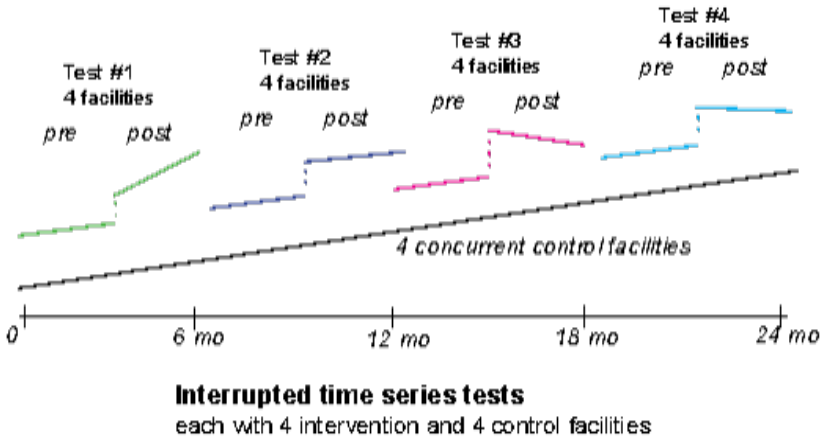

Figure 8: Interrupted time series experiment design and timeline

12.3.2) INTERVENTION DETAILS

There will be four strategies or bundles of strategies tested, one bundle in each of the four interrupted-time series evaluations. Three of the bundles of strategies will be determined based on the qualitative information gathered

in Aim 1 by stakeholders and are unknown at this time. One bundle of strategies is pre-developed and includes 3 components: video-based PrEP counselling, HIV Self-Testing [HIVST] for women undergoing repeat HIV testing, and optimized PrEP delivery and prescription processes (Figure 9). We will work with a videography company to develop the video-based PrEP counseling component. We will borrow processes from ongoing and recently completed studies in western Kenya related for optimizing PrEP dispensing and HIVST while clients wait. PrEP will be stored in MCH clinics. Once women ask for PrEP and have been confirmed eligible, women will receive PrEP at MCH clinic. In our prior work, we have arranged with pharmacy and CCC to maintain supplies of PrEP at MCH. HIVST will be provided as an option in private cubicle-style kiosks, which have been tested in western Kenya and found to be acceptable and feasible.

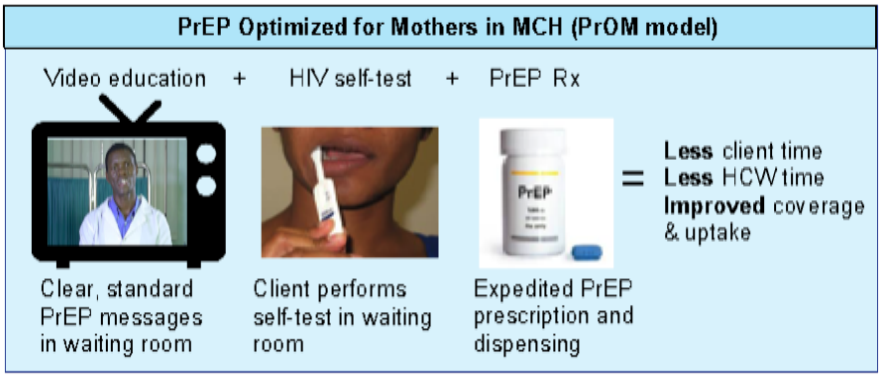

Figure 9: Pre-determined bundle of implementation strategies

12.3.3) STUDY POPULATIONS

The twenty (20) health care facilities that were included in Aim 1 surveys will be included in the implementation and evaluation of PrEP optimization strategies identified through Aim 1 activities. Of the 20 facilities, facilities will be assigned one of four intervention groups (4 facilities per group) or a comparator group (4 facilities) throughout the four interrupted-time series rounds. Up to twenty HCW will be approached at each facility per interrupted time series cycle to participate in a satisfaction survey to understand their experience with the PrEP optimization intervention.

During each of the four interrupted-time series rounds, we will abstract all clinical records for HIV-negative patients receiving MCH services to assess penetration of PrEP screening and PrEP uptake. We anticipate abstracting records for up to 200 clients per month per clinic (1,200 abstracted records per facility per interrupted-time series). Additionally, to assess intervention fidelity and client satisfaction through exit surveys with up to 40 clients per month per facility (240 exit surveys per facility per ITS). We will assess client time using client observation with up to 200 clients per clinic per interrupted-time series cycle.

12.3.4) SAMPLE SIZE DETERMINATION AND FORMULAS USED

To maintain the greatest amount of power, outcome estimates will be based on individual count data, not aggregated to summaries. We utilized Stata 14 for sample size calculations.

- Time period: Each experiment will include 3 months of data before each strategy is introduced and 3 months after each strategy is introduced
- Sample size (facilities): There will be 4 experiments, each will include 4 intervention facilities (16 facilities) and the same 4 comparator facilities; for a total of 20 facilities.
- Sample size (participants): We will observe 200 clients per clinic per experiment. We will collect survey data from 240 clients and 20 HCW per clinic per experiment. We will abstract register data during each experiment; while we are unable to predict total number of records to be abstracted, we expect abstraction of ~200 clients per month per clinic.
- Assumptions: α=0.05, two-sided tests, a conservative harmonic mean of 100 women presenting to ANC per month (~600 women over 6 months) per cluster (mean in PrIYA sites was ~163 per month), and a conservative estimate of the coefficient of variation of 0.5. We assume that penetration of PrEP screening and counselling is 68% (SD: 18%), time spent by HCW on PrEP services is 18 minutes (SD: 8 minutes) per PrEP initiator and 13 minutes (SD: 6 minutes) per PrEP-non-initiator, uptake is 10.5% (SD: 5%), and that knowledge and satisfaction scores are on a 100-point scale and have an SD of 20.

- Detectable effect size: We will be able to detect an absolute change of +/-4.8% for outcomes of penetration of PrEP screening, an absolute change of +/- 2 minutes in time, an absolute change of +/1% in PrEP uptake, and an absolute difference of 4 points in knowledge and satisfaction scores.
- Power: We will have at least 80% power

12.3.5) RECRUITMENT PROCEDURES

Register abstraction: We will not actively recruit individual participants for register abstraction.

Client observation: Women receiving MCH services will be approached as they enter the facility and asked to carry a time card. Each time card will collect the time that each service starts and ends and will be filled by providers, but will not collect any identifying information. Study staff will be posted at each facility until the sample size is reached.

Surveys with clients: Women receiving MCH services will be approached as they exit the facility and asked to participate in a brief survey. Study staff will be posted at each facility until the sample size is reached.

Surveys with HCW: HCW providing services will be approached by study staff in person, by phone or email and invited to complete a survey.

12.3.6 ENROLLMENT & STUDY PROCEDURES

Register abstraction

Consent: Individual patients will not be asked to provide consent as abstracted data are anonymous and it would not be feasible to contact clients to seek consent.

Procedures: We will abstract anonymous patient level count data from health registers at all of the intervention and comparator facilities. We will abstract the following count data from registers: women screened for PrEP interest (penetration), women offered HIV testing and PrEP (fidelity), women who initiate PrEP (uptake), women who adhere to PrEP (adherence determined via pill count), and women who refill PrEP (continuation).

Client observation

Consent: Individual patients will be given the opportunity to verbally accept or decline to carry cards; data are anonymous.

Procedures: A trained research assistant will conduct flow mapping (physical walk throughs to graphically represent patient flow pathways in a facility) and conduct time-and-motion data collection (counting minutes spent waiting and receiving various services) to describe the flow of women within health facilities and between providers as they receive services. Individual patients will be given the opportunity to carry a single sheet of paper with a study identification number to each service delivery point. Health care workers or research assistants will note the time that services begin and end. We will characterize the following outcomes: efficiency and time spent by HCW and clients.

Surveys with clients

Consent: Women will be given the opportunity to provide oral informed consent for participation or to decline participation; these surveys are anonymous.

Procedures: Women will complete a survey following service delivery completion. The following data will be collected via survey: client satisfaction with services, client PrEP knowledge, client perception of being offered PrEP services.

SARA Surveys with HCW

Consent: HCW will be given the opportunity to provide oral informed consent for participation or to decline participation; these surveys are anonymous.

Procedures: HCW will complete a survey. The following data will be collected via survey: HCW satisfaction with training and service delivery modifications.

Planned Analyses: We will use interrupted time series methodology to compare changes in penetration (PrEP screening), uptake (PrEP initiation), adherence, and continuation (PrEP refills) between the baseline and intervention periods for intervention facilities and with the comparison facilities.

12.3.7) LABORATORY METHODS

Not applicable

12.3.8) DATA COLLECTION INSTRUMENTS

- Exit Survey
- Record abstraction form

12.3.9) VARIABLES: Outcomes, indicators, and source documents

Outcome	Indicator	Source documents
PrEP penetration	Proportion of women who are screened for PrEP / total women receiving antenatal or postnatal services	Routine program data; PrEP register, antenatal register, postnatal register, family planning register
PrEP fidelity	Proportion of women who receive all PrEP specific steps in a visit: HIV testing, HIV risk screening, PrEP counseling	Primary data of anonymous exit survey assessing services received Direct observation of client-provider interactions Routine program data: HIV testing register, PrEP register, antenatal register, postnatal register, family planning register
PrEP uptake	Proportion of women who accept PrEP among those offered	Routine program data: PrEP register
PrEP continuation	Proportion of women who present for a refill among those initially prescribed PrEP	Routine program data: PrEP register, pharmacy records
PrEP adherence	Proportion of women who have >80% adherence to PrEP by pill count among those initially prescribed PrEP	Routine program data: PrEP register, pharmacy records
PrEP efficiency	Patient flow mapping to identify more efficient client flows with fewer transitions between physical spaces and providers	Primary data collection through direct observation of patient flow
Timeliness	Time and motion data to assess wait times, service delivery times, and HCW burden	Primary data collection through direct observation and time collection
Client satisfaction	Satisfaction on a scale of 1-10 adapted from *Training Satisfaction Survey*	Primary data collection through anonymous surveys
HCW satisfaction	Satisfaction on a scale of 1-10 adapted from *Training Satisfaction Survey*	Primary data collection through anonymous surveys
Client PrEP knowledge	10 questions based on content covered in counseling sessions	Primary data collection through anonymous surveys

12.3.10) TRAINING PROCEDURES

Dr. John Kinuthia will oversee training of study staff on PrEP optimization procedures, exit surveys, and record abstraction. Trained study staff will work with facility staff at all facilities to ensure appropriate implementation of ITS-specific PrEP optimization procedures.

12.3.11) STUDY MATERIALS

- Oral consent guide

12.4 AIM 3:

To review evidence, findings, and understanding of study findings through two stakeholder workshops and to evaluate these workshops through IDIs and surveys.

	Aim 3
	Stakeholder views on research findings and best practices
Population	PrEP policymakers, implementers, frontline HCW, PrEP ambassadors, community advisory board members
Design	Qualitative cross-sectional design
Data collection	IDI, facilitated workshops
Sample size	PrEP policymakers: up to 15 IDIs
	Workshop participants: up to 50 participants
Outcome(s) of interest	Decision-making process and understanding of budget impact analyses, consensus-determined best practices for PrEP delivery and integration
Inclusion criteria	PrEP policymakers and implementers: involved in making decisions related to PrEP at national or county level, ≥18 years
	Other stakeholders: stakeholder in in PrEP delivery, ≥18 years; adolescent PrEP ambassadors, ≥15 years
Exclusion criteria	N/A

12.4.1) STUDY DESIGN

PrEP policy makers, implementers, and other stakeholders will be invited to participate in a series of workshops aimed at identifying priority interventions to test for PrEP optimization, review findings of the interrupted time series intervention testing, draft a document of best practices for PrEP implementation, and review budget impact analyses. At the final workshop, cognitive interviews will be conducted with stakeholders to understand how they interpret and understand the budget impact analysis.

12.4.2) STUDY POPULATIONS

Stakeholder meeting to develop best practices

PrEP policy makers, implementers, and other stakeholders will be identified through consultation with national and county level ministry of health officials. We will ensure that each workshop includes up to 50 participants representing a range of stakeholder perspectives and experiences, at least:

- 5 national level policy makers
- 5 county level policy makers
- 5 facility level policy makers

In aligning with core principles of community engagement and ensuring voices of all key stakeholders are represented, including potential end users and those within the community of practice [62], we will purposively invite adolescent PrEP ambassadors, frontline HCWs, implementing partner organizations, representatives from the National AIDS and STD Control Program (NASCOP), and County health officials to participate in the Best Practices Development Workshop. Representatives from stakeholder groups will be identified through informal discussions with MOH and County Health officials, Community Advisory Board members, PrEP implementers and peer-reviewed published articles or presentations from local, regional or international conferences.

12.4.3) SAMPLE SIZE DETERMINATION AND FORMULAS USED

Stakeholder meetings to develop best practices:

We will conduct 1 workshop with up to 50 participants representing a range of stakeholder perspectives and experiences. Based on a previous workshop conducted in this region with diverse stakeholders from various cadres who engaged with formative research materials, this number of participants is sufficient to reflect a range of experiences and priorities, but small enough to facilitate crucial interactive activities; we predict that this sample size will additionally be sufficient to reach theoretical saturation, that no new themes are identified with each additional individual.

Budget impact analysis review:
We will conduct a series of 15 semi-structured, in-depth interviews with policymakers. Based on previous studies in this region, we predict that 15 IDIs will be sufficient to reach theoretical saturation, that no new themes are identified with each additional IDI [59].

12.4.4) RECRUITMENT PROCEDURES

We will conduct a working meeting with an estimated 50 selected HCWs and policy makers from throughout Kenya with expertise PrEP delivery and MCH services. HCWs with significant experience in assisting PrEP delivery and/or MCH services will be purposively recruited from high performing clinics from Aims 1 and 2. We will also recruit healthcare workers known for their work in PrEP and MCH through reviewing peer-reviewed published articles or presentations at scientific meetings.

HCWs and policy makers participating in the working group will be purposively selected and contacted by phone, email or in person by study staff. They will be told the details of the working group, including its purpose and scope of work. A script outlining talking points used for recruitment is attached as an appendix. Those willing and eligible to participate will be asked to give written consent to be part of the working group and have the discussions audio recorded and information about the process written up into a publishable manuscript. It will be emphasized that participation is completely voluntary and opting not to participate will have no repercussions on the HCWs employment. They will read through the consent form on their own. One of the study personnel will then go through it with them verbally and answer any questions they might have. Those who consent will participate in the workshop with study staff to refine and adapt the transition tools. All participants will provide their contact information (phone, name, email if necessary) for follow-up until the working group meeting is conducted.

12.4.5) ENROLLMENT & STUDY PROCEDURES

Stakeholder meeting to develop best practices:

Consent: Stakeholders will be invited to provide written informed consent for participation in this workshop.

Procedures: A best practices document will be developed and refined during a 2-day workshop. The workshop will be aligned with community-based participatory research and community engagement practices [63], including developing a shared vision, collaboratively identifying goals, and meeting the objective of developing trusting and sustainable relationships between all stakeholders to ensure long-lasting impact and improved health outcomes.

Data from Aims 1 and 2, as well as past learning from the PrIMA and PrIYA projects, will be compiled into brief reports synthesizing key elements of PrEP provision through MCH and FP clinics in Kenya. Reports will include information on client demographics, PrEP uptake and access experiences, challenges in PrEP delivery across ecological levels, and employed implementation strategies and identified implementation strategy domains.

The Best Practices Development Workshop will be conducted over 2 days. Aligning with previously conducted best practices and intervention development processes [64–66], the workshop will include small and large group deliberative processes designed to maximize opportunities to hear all stakeholder views. To ensure accurate portrayal of stakeholder input, all large and small group sessions will be audio recorded and reviewed during final best practices development processes. Final workshop sessions will focus on implementation planning, addressing key steps towards implementation found in the Guideline Implementation Planning Checklist [67]. We will also conduct an evaluation of the best practices development process using post-development workshop questionnaires, focusing on 3 key process outcomes: recruitment, context, and satisfaction [64].

Budget impact analysis review:

Consent: Policymakers will be invited to provide written informed consent for participation in semi-structured in-depth interviews.

Procedures: During the interviews, policymakers will be asked to narrate their thoughts aloud, borrowing methodological approaches from cognitive interviewing, a technique used in psychology to assess comprehension [68].

Question guides will cover the following topic flow: 1) factors that influence policymaker's current approach to making a decision about whether or not to adopt a new intervention into their clinic/county/national program, 2) current approach to considering cost data, budget impact, and cost-effectiveness data in their decision-making. Midway through the interview, a hypothetical vignette will be introduced, in which the policymaker is asked to consider adopting PrEP delivery integrated into ANC, either with or without additional implementation strategies from Aim 2, into their clinic/county/national program. Initially, information will only be provided about effectiveness in terms of penetration of PrEP screening. The interviewer will then assess: 3) factors that influence the policymaker's initial decision about whether or not to adopt the intervention. Then the results from the budget impact analysis will be shared in printed form, supplemented by standardized explanatory scripts, and the interviewer will assess: 4) policymaker's understanding of the results, 5) any changes to policymaker's initial decision regarding adoption of PrEP provision integrated into ANC.

Planned Analyses:
Stakeholder workshop: We will use a facilitated workshop in order to identify best practices for PrEP implementation in MCH and FP settings. Key themes from the workshop with be documented and summarized into a PrEP implementation best practices report.

Budget impact analysis: We will use qualitative methods to explore policymaker approaches to decision making with limited resources.

12.4.6) LABORATORY METHODS
N/A

12.4.7) DATA COLLECTION INSTRUMENTS
- Workshop Evaluation Survey
    - Workshop participant demographic survey

12.4.8) TRAINING PROCEDURES
Drs. Beima-Sofie and Wagner will oversee the training of study staff on workshop procedures and oversee the workshop.

12.4.9) STUDY MATERIALS:
Workshop consent
- Recruitment Script
- Workshop topic domains overview

13) QUALITY ASSURANCE PROCEDURES
Adherence to protocol: Weekly reporting of enrollment, IDIs/FGDs transcript completion, and data 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.

Data Quality: A dedicated data team will be responsible for data collection using an electronic data collection platform, RedCAP. The data team will communicate weekly with the operations team and leadership including reporting on data cleaning, study monitoring, and interim analyses.

14) ETHICAL CONSIDERATIONS

14.1 ASSESSMENT OF RISKS AND BENEFITS

i) ADEQUACY OF PROTECTION AGAINST RISKS

Participants may feel discomfort in the questions they are asked during the FGDs, IDIs, and surveys. All participants will be informed that they do not have to answer any questions they do not want to answer. Additionally, there may be a breach in confidentiality of participants. We are taking all necessary precautions to prevent a breach in confidentiality, including storing materials that could identify participants in locked files, and storing all participant information in encrypted locations.

ii) POTENTIAL BENEFITS OF PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Health care workers and women clients will not directly benefit from the proposed research. PrEP policy makers and implementers may benefit from the best practices and budget impact analysis activities as it will provide information that can inform their jobs.

iii) IMPORTANCE OF THE KNOWLEDGE GAINED

Information gained through this study will result in improved PrEP delivery to women receiving MCH services, while also optimizing health care worker resources.

15) DATA MANAGEMENT AND STATISTICAL ANALYSIS PLANS

All data for this project will be managed at the Kisumu study office and the University of Washington in Seattle. Participants will be identified according to unique identification numbers—no identifying information will be captured or stored in this study, except the information needed for scheduling purposes or re-contacting to verify data accuracy. All qualitative data collected through interviews and focus groups to address Aim 1 and Aim 3 will be stored on a secure server. All recording devices will be wiped clean after recordings are uploaded to the secure server.

All quantitative data collected through surveys to address Aim 2 will also be stored on a secure server. Quantitative data collected during the course of this study will be collected electronically via REDCap data collection software. Data will be uploaded daily via REDCap Mobile App from tablets to the REDCap 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.

a) Data Ownership

The proposed project is a collaborative effort between investigators at the UW and KNH. The aforementioned institutions will jointly share ownership of the data. Study investigators at the UW 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.

b) Data Release/Sharing Policy

All quantitative data collected as part of this proposed research project will be made available to access or download files on a study related website (URL to be determined) following ERC approval for data sharing and agreement to the data sharing agreement. 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.

c) Data Monitoring Committee

Prior to study initiation, we will convene a data monitoring committee (DMC) to review study aims, statistical analysis plan, and protocol. An annual DMC will be held during Aim 2 activities will be conducted to assess interim outcomes.

16) STUDY LIMITATIONS AND HOW TO MINIMIZE THEM:

Interrupted time series designs do not have as strong protection against confounding as randomized trials. Cluster randomized trials were not feasible or reasonable at this stage of scientific discovery. We considered alternative quasi-experimental designs (classical pre-post, difference in differences, regression discontinuity, stepped wedge), but none provided as strong control for temporal trends or heterogeneity between clinics. We considered adaptive designs, but wanted to isolate the individual, rather than additive or sub-group level, impact of the implementation strategies.

We hope to gain insights on improving efficiencies for PrEP delivery in MCH and FP clinics based on views from a group of stakeholders with broad expertise. MCH and FP clinics in Kenya face unexpected events (specifically, health worker strikes and implementation of universal health care [UHC]) that may influence HCW and client views on PrEP implementation and may challenge the intervention pilot. Our team has been able to work around these challenges in the past, liaising with private sector MCH/FP clinics (during public sector strikes) and overtly addressing new challenges such as UHC as part of process of stakeholder engagement. Stock-outs of self-tests or PrEP could challenge implementation of the pre-designed HIVST model; however, we have been assured that there is sufficient supply of PrEP and HIV self-tests in Kenya and that studies such as the one we propose are of high priority nationally and regionally in Kenya for use of these commodities.

During direct observation, such as that employed for time-and-motion data collection, there is the possibility of the Hawthorne effect, in which individuals modify their behavior because they are observed. This is typically a concern with shorter data collection periods; these data will be collected over a series of approximately 2 weeks, so we anticipate a more limited or negligible Hawthorne effect. There is no potential benefit for the individuals being observed to modify their practices since the evaluation of is of the health system in general rather than a specific behavior.

17) TIMELINE/ TIME FRAME:

		2019	2020				2021					
		Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Protocol development and ethics approvals		x										
Study start up												
	Video development	x	x									
	Develop training materials	x										
	Train team		x									
	Sensitization meetings		x									
Aim 1: Identify and quantify innovations												
	Identify & sensitize facilities		x									
	Qualitative data collecttion			x								
	Quantitative survey completion			x								
	Data analysis & manuscript development				x	x						
Aim 2: Intervention testing												
	Experiment round 1				x	x						
	Experiment round 2						x	x				
	Experiment round 3								x	x		
	Experiment round 4										x	x
	Data analysis & manuscript development											
Aim 3: Stakeholder Workshop												
	Identify & recruit participants											
	Hold workshop											
	Analyze results and disseminate results											

18) HUMAN SUBJECTS

a) Ethical Approval

We will obtain ethical approval from the University of Washington (UW) Human Subjects Division (IRB) and Kenyatta National Hospital-University of Nairobi (KNH-UoN) Ethics and Research Committee (ERC). There will be minimal risk to the participants taking part in this study. Any changes to the protocol will be submitted to the UW IRB and KNH-UoN ERC.

b) Collaborating sites

The study will be conducted in collaboration with the UW, KNH, and NASCOP. 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.

c) Informed Consent

We will obtain electronic written informed consent for participation in all in-depth interviews, focus groups and HCW surveys that occur under Aim 1. The consent will explain to each potential participant the purpose, risks and benefits of the study. Participants will be informed that they can choose to withdraw from the study at any point and for any reason. They will also be informed that participation is completely voluntary. Participants will be offered a copy of the consent form to keep and will be informed that their role will end after they complete either the in-depth interview, focus group, or survey. Participants who agree to participate in study activities will sign the informed consent form using the electronic consent module through RedCap. This will allow for electronic collection of consent signatures, allowing for realtime consent quality monitoring, as well as secure, encrypted, storage of participant names and signatures. Identifying information on participants will only be collected during the informed consent process.

For exit interviews during Aim 2 activities, we are requesting a waiver of written consent. The purpose of these interviews is to assess knowledge and satisfaction for the PrEP optimization approaches. Data collectors will approach women as they exit the facility, explain the purpose of the survey, and ask whether they are willing to answer a few questions. A waiver of written consent is requested as there will be no identifying information of the participants. The guide for obtaining oral consent is included in the consent material appendix.

IDIs and surveys will be verbally administered to ensure participants who cannot read or write are still able to participate in this study.

Comprehension: Participants who do not consent in the presence of study staff (for example, prior to self-administered electronic surveys) will be given the phone number of study staff and will be encouraged to call if they have any questions about the consent or study.

Study staff will review the informed consent information with each study participant when consenting is conducted in-person. Study staff will also ask participants a 2-3 questions to assess understanding. Questions may include:

1. What is the purpose of this study?
2. When can you decide not to participate in this study?
3. Will we record your voice during this study?
4. Will we access your medical records during this study?

Waiver of written consent for data extraction

Register abstraction: For aims that involve register abstraction, we are not planning any direct contact with patients. We will exclusively abstract data from registers and medical records without abstracting any personally identifiable information or constellation of variables that could personally identify individuals. The study data clerk will review health registers and medical records and will abstract simple count data about the number of individuals who complete each step. While registers and medical records may contain personally identifiable data, study data clerks will not abstract any of these variables, nor any constellation of variables that could be

personally identifiable. We are requesting a waiver of informed consent to abstract medical records from this population.

Waiver of parental permission for 15-17 year olds

The age of majority in Kenya is 18 years. For adolescent girls, ages 15-17 years, we are requesting a waiver of parental consent for participation based on the following points:

1. Adolescents are able to provide consent (parental consent can be waived) for HIV and STIs testing and treatment in Kenya). However, parental involvement is always desirable and adolescents would be able to choose whether they want to have parents involved in the decision of whether or not to provide consent, and participate in the study.
2. If there are confidentiality issues regarding adolescents discussing personal HIV testing or sexual activity with their parents, requiring parent consent could breech confidentiality of the adolescent.
3. Recent Kenya Demographic Health Surveys have allowed sexually active adolescents to participate in national surveys, which allows this marginalized population to be represented and their data used to help guide public health programs and policies.
4. Excluding adolescents from the study would be denying them an opportunity to participate in research to improve PrEP delivery in FP and MCH clinics. Allowing adolescents the opportunity to provide their own consent is in alignment with the ethical principles of justice, beneficence, and autonomy.

d) Handling Adverse events

We do not anticipate any significant adverse events to occur throughout this study as the goal of this study is simply to understand barriers and facilitators to PrEP adherence. However, in the event that an adverse event occurs, participants will be given contact information for study team members. All unanticipated problems will be reported to the PIs and ethics committee according to UW, KNH, and KNH ERC guidelines.

19) BUDGET (total budget period)
20) LIST OF ABBREVIATIONS
21) LIST OF APPENDICES/ATTACHMENTS

Appendix A: Consent Forms

- HCW Consent Form
- Policy Maker IDI Consent Form
- PrEP User FGD Consent Form
- Exit Survey Oral Consent Guide
- Workshop Consent form

Appendix B: Summary of Key Themes from Data Collection Tools
Aim 1:

- PrEP user focus group guide
    - Starting PrEP
        - Factors that lead to the decision to start PrEP
        - Experience at the facility
        - Information received from clinic staff
    - Using PrEP
        - Duration of PrEP use
        - How PrEP use has impacted the participant
        - Plan for future PrEP use
    - PrEP delivery
        - What is their clinic doing well? How can the clinic improve?
        - Advantages of PrEP delivery through MCH/FP clinics

        - Advice for PrEP delivery through MCH/FP clinics
- PrEP user demographic information
    - Gender
    - Age
    - Education
    - Employment
    - Living situation
    - Partner characteristics
    - Children
    - PrEP use and experience
- HCW Survey
    - Employment
        - Location
        - Title
        - Experience
    - Education
    - Age
    - Gender
    - PrEP training
    - PrEP experience
    - PrEP delivery strategy preferences
    - Impact of COVID-19 on PrEP delivery and clinic duties
    - Transition of PrEP delivery from research to clinic staff
    - HCW daily experiences
- HCW FGD guide from CFIR Interview Guide, Themes include:
    - Intervention Characteristics
    - Outer/External Setting
    - Inner Setting
    - Characteristics of Individuals
    - Process
- Service Availability and Readiness Assessment Tool Survey
    - Work health organization tool for measuring health system strength. Key themes:
        - Service availability (facility density, health care worker density, service utilization)
        - Service readiness (basic amenities, equipment and supplies, diagnostics, essential medicines, and commodities)
        - Specific Service readiness in family planning, antenatal care, HIV, and PMTCT
- PrEP policy maker and implementer interview guide
    - Demographic information
        - Age, gender, role, county, years of experience, experience with PrEP
    - PrEP delivery
        - What is working well for PrEP delivery?
        - What are existing challenges?
    - PrEP in MCH/FP
        - Should PrEP be delivered in MCH/FP clinics? Advantages? Disadvantages?
        - Strategies for improving efficiency
        - Barriers to delivery

Aim 2:

- Exit Survey
    - Age
    - HIV Status
    - Assessment of risk behaviors and PrEP at clinic visit today
    - Risk profile

        - Did you engage in any of the following in the last 6 months? Yes/No (Participant will not have to disclose WHICH risk behavior)
    - PrEP counselling
    - PrEP knowledge questions
- Data Abstraction Tool
    - Collect data on PrEP screening, prescription, and discontinuation disaggregated by gender and age

Aim 3:

- Workshop Evaluation Survey
    - Satisfaction with workshop
    - Context of workshop

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