Evaluation of oral pre-exposure prophylaxis (PrEP) implementation in public HIV care clinics in Kenya

Elizabeth M. Irungu,

A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2021

Reading Committee

Jared M. Baeten, Chair

Deborah Donnell

Nelly Mugo

Kenneth Mugwanya

Gabrielle O'Malley

Program Authorized to Offer Degree:

Global Health

University of Washington

Abstract

Evaluation of oral pre-exposure prophylaxis (PrEP) implementation in public HIV care clinics in Kenya

Elizabeth M. Irungu

Chair of the Supervisory Committee:
Jared M. Baeten, Vice Dean, School of Public Health
Professor, Departments of Global Health, Medicine, and Epidemiology

Daily, oral pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) is a highly potent HIV prevention intervention with potential to reduce HIV incidence among populations at risk of HIV in Africa if delivered with sufficient coverage. There are extensive data from high-income countries describing diverse settings in which PrEP services are offered. However, data describing PrEP scale-up models in low- and middle-income countries are limited.

Public HIV care and treatment programs in Africa have been very successful at scaling up antiretroviral therapy (ART) over the last 15 years and are an attractive choice for integration of PrEP delivery. The main objective of the work described in this dissertation was to evaluate the effectiveness of PrEP implementation and integration in public HIV care clinics. The specific aims include to 1) conduct a step wedge cluster randomized trial of PrEP integration in public health HIV care clinics (the Partners

Scale-Up Project) and evaluate impact; 2) conduct a process evaluation of PrEP integration in public HIV care clinics in Kenya, focusing on adaptation; 3) develop and evaluate the effectiveness of an on-site modular training approach to amplify the number of health care providers trained to deliver PrEP in public HIV care clinics in Kenya; and 4) summarize early PrEP rollout in African settings, challenges encountered and opportunities to expand implementation.

We found evidence that integration of PrEP in public HIV clinics was feasible. By improving the capacity of health providers in those care clinics to offer PrEP services through training and technical support, PrEP uptake increased more than 20-fold and was sustained. With existing personnel and infrastructure, the high-volume HIV care clinics efficiently reached partners of HIV infected persons and other populations at HIV risk. PrEP users had reasonable continuation rates and objective evidence of high adherence. Using qualitative methods, we found that clinics made pragmatic, effective adaptations to non-core components of PrEP delivery services and to their routine practice to address challenges in PrEP delivery. We established that clinics that instituted some of the adaptations had above average monthly PrEP initiation and continuation rates. To amplify PrEP delivery in public health facilities, we developed and evaluated an innovative on-site modular training approach. We found that this approach was acceptable and it enabled many health providers to receive PrEP training conveniently and at a relatively low cost. Finally, our summary of early PrEP roll out in Africa revealed that there was high interest in PrEP among all populations at risk of acquiring HIV, but individuals did not continue use as expected. We suggested

strategies to make PrEP delivery efficient, including delivery within community pharmacies, use of peers, services availed in low tier facilities and exploration of one-stop services to make PrEP delivery less burdensome.

The collective results presented in this dissertation illustrate that integration of PrEP services in public HIV care clinics in Kenya is a successful and sustainable model for PrEP implementation. We posit that this model can be scaled up in African countries planning to set up PrEP programs.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

This dissertation would not have been possible without the support of my family, colleagues, and mentors.

I am extremely grateful to members of my doctoral committee, Drs. Jared Baeten, Dave Grembowski, Deborah Donnell, Nelly Mugo, Kenneth Mugwanya and Gabrielle O'Malley for generously sharing their time and knowledge over the last three years. I am especially grateful to my advisor and Chair of my dissertation committee, Prof. Jared Baeten, who has been a tireless mentor and advocate for close to 10 years. He always made time to meet weekly, regardless of the time zone we were in, made sure I was making progress, however small, and gave me the platform in which to grow as a HIV prevention scientist. I have been extremely fortunate to have worked with him.

I sincerely thank the team at PHRD Kenya, led by Dr. Nelly Mugo, for being an incredible place to work and do science and have fun while at it. The Partners Scale-Up Project staff in Thika and Kisumu have taught me so much about working with public health facilities.

I am grateful to Nelson and Naomi, my parents, and siblings (Njeri, Karong'a and Kamau), who gave me lots of encouragement and celebrated my every win. Lastly, I am indebted to my husband, Njagi Njogu, who has provided unwavering support, and unconditional love and understanding as I have worked on this dissertation.

Great is thy faithfulness, oh God, my Father.

DEDICATION

To our children, Njogu and Irungu

Chapter 1: Introduction

In 2019, close to sixty percent of the 1.7 million new HIV infections globally were in sub-Saharan Africa, making HIV prevention a priority in this region.[1] Antiretroviral based HIV prevention interventions - including use of ART by persons living with HIV and PrEP by those at risk of acquiring HIV – have potential to reduce HIV incidence markedly if implemented effectively.[2] In randomized controlled trials conducted in multiple geographical locations, including sub-Saharan Africa, daily tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (FTC) reduced HIV transmission by over 90% among people who were adherent, establishing that oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention intervention.[3-7] Increasing evidence from open-label PrEP studies and demonstration projects has demonstrated high levels of protection against HIV and great willingness to use by people at risk of acquiring HIV.[8-11]

The World Health Organization in 2015 issued strong recommendations for use of PrEP as a prevention choice for people at substantial risk of HIV infection. Many countries in Africa have adopted this recommendation and have begun implementing PrEP programs.[12-14] The Kenyan Ministry of Health revised its guidelines in 2016 and launched a national PrEP program in May 2017. PrEP is recommended for HIV uninfected persons with substantial on-going risk, including uninfected partners in HIV serodiscordant partnerships, those with multiple partners or engage in transactional sex, those who use injection drugs and those who have inconsistent use of condoms with partners of unknown HIV status, among others.[15] The guidelines recommend rapid HIV testing quarterly and a creatinine test as baseline and annually thereafter. Other

recommended baseline tests are HBsAg and HCV serology. In its PrEP implementation framework, the Kenyan National AIDS and STI Control Program (NASCOP) proposed public health HIV care clinics, drop-in centers, ante-natal and family planning clinics and community settings as some of the locations for delivery of PrEP services. [16,17]

PrEP implementation in HIV care clinics

Public HIV care clinics in Kenya successfully serve over one million people living with HIV, providing regular clinical and laboratory monitoring and prophylaxis and treatment of opportunistic infections. These clinics present features that are favorable to PrEP scale up.[18-20] First, public HIV care clinics offer HIV prevention services including regular risk reduction counselling, HIV testing services and condoms to uninfected partners of persons living with HIV, thus providing a ready population that could benefit from PrEP services. Second, health workers in these clinics are conversant with prescribing and counselling on antiretroviral medication use. Third, these clinics also have an established commodity management system for antiretroviral medications and HIV test kits. However, long waiting times due to understaffing, HIV-related stigma, frequent commodity stock outs, high staff turn-over and poor infrastructure may pose challenges to efficient PrEP delivery in a public HIV care clinic.

Data on strategies that foster efficient, effective scale up of PrEP services in public HIV care clinics are limited. This dissertation contributes to closing this gap. The Partners Scale-Up Project is an implementation science project that aimed to catalyze delivery of PrEP by training health care providers on PrEP service delivery and providing on-going technical assistance and mentoring of providers in 25 public health HIV care clinics.[21]

Using an implementation science approach, we evaluated the effectiveness of PrEP implementation and integration in these HIV care clinics. We assessed PrEP uptake and use, fidelity to core components of the PrEP program and adaptations made by HIV clinics to the program guidelines and to their routine practices to overcome implementation challenges. We also designed, implemented and evaluated a novel on-site modular training approach to expand PrEP delivery to other health facilities.

Chapter 2: Integrating pre-exposure prophylaxis services into public HIV care clinics in Kenya: Results from a pragmatic stepped-wedge randomized trial

---

Will partners of people living with HIV and other high-risk individuals will initiate PrEP at public HIV care clinics, be adherent and will continue to use PrEP while they are at risk?

To provide real-world evidence of PrEP implementation in public HIV clinics in Kenya, and within Kenya's national PrEP program, we conducted an implementation trial of PrEP service delivery in 25 HIV care clinics using a prospective pragmatic step-wedge cluster randomized design. In consultation with NASCOP and county level health officials, we identified 25 high volume public health HIV care clinics in western (former Nyanza province) and central (including former Central and Nairobi provinces) regions of Kenya, regions with high to medium level HIV incidence. The interventions employed were health care worker training on PrEP and providing technical assistance to health

providers. All PrEP provision was done by clinic staff without additional financial support.

In chapter 2, we examine the impact of building capacity of health workers through PrEP training and technical assistance on PrEP uptake, adherence and continuation. Our results provide evidence that integrating PrEP programs into public HIV care clinics in Kenya is feasible. We observed high, sustained PrEP uptake by individuals at risk of acquiring HIV following the interventions, reasonable continuation, high adherence among those returning for refills, frequent PrEP restarts, and low HIV incidence. Importantly, providing PrEP services within existing HIV service delivery programs did not significantly alter the workload.

Chapter 3: Process evaluation of PrEP implementation in Kenya: Adaptation of practices and contextual modifications in public HIV care clinics

---

Will public HIV care clinics in Kenya make pragmatic, effective adaptations to facilitate integrated delivery of PrEP?

HIV care clinics often make adaptations and modifications to ART interventions to address shortcomings in service delivery.[22-26] Public health facilities providing ART services in the region make major modifications to ART interventions to improve their capacity to serve more clients despite being resource constrained.[27] The modifications include reducing frequency of refill visits, implementing pharmacy-only refill visits and task shifting. Fidelity to core components of a health intervention (i.e., the degree to which a program is delivered as intended) is determinant of attainment of impactful

health outcomes. [28,29] However, since public HIV care clinics are unique service delivery points as they serve the HIV infected populace and face heavy work load and severe staffing shortages, making adaptations to non-core elements of the PrEP program and modifications to the clinic settings to facilitate service delivery may be necessary. Such adaptations would help the program meet the needs of the target population, local clinic circumstances and culture. Furthermore, the Consolidated Framework of Implementation Research (CFIR) details adaptability of the intervention as one of the determinants of successful uptake of intervention.[30]

Chapter 3 details the specific adaptations made by public HIV care clinics in Kenya and their impact on the success of PrEP delivery services. Using qualitative methods, we analyzed health provider interviews and technical assistance reports to identify clinic level adaptations and reported them guided by the expanded framework for reporting adaptations and modifications (FRAME).[31] We report that health providers made innovative adaptations to activities detailed in PrEP guidelines and instituted modifications to routine practices. These changes were made to simplify PrEP delivery processes for clients and to reduce service delivery barriers among health workers.

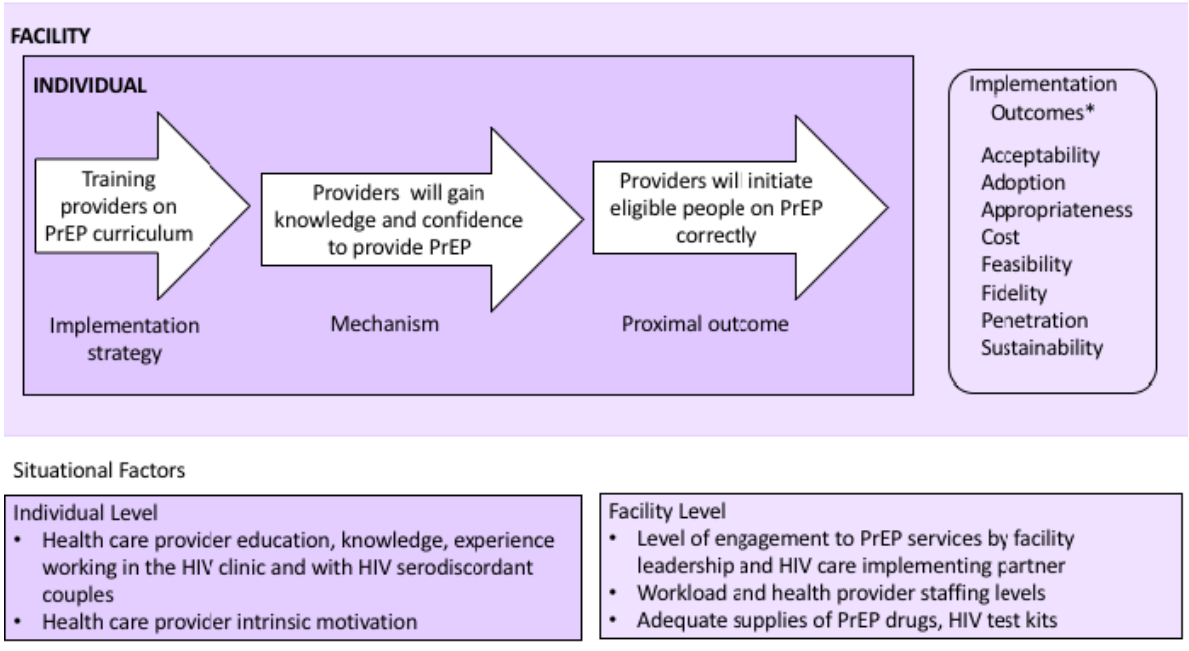
Chapter 4: Using an on-site modular training approach to amplify PrEP service delivery in public health facilities in Kenya

---

Will the on-site modular training approach be an acceptable, low-cost approach that will amplify the number of providers able to deliver PrEP services in the country?

Surveys conducted among health providers in high income countries have demonstrated that limited knowledge about PrEP is a major barrier to issuing prescriptions [32-34], and training increases their likelihood to prescribe PrEP.[35] Since PrEP is a bio-behavioral intervention PrEP, health provider awareness, knowledge and competence in delivering PrEP services is key to adoption and implementation with fidelity of the PrEP program in public health facilities (*Fig 1*).

Fig 1: Training evaluation framework



Providers require training and mentorship to help them correctly identify people at risk of acquiring HIV and thus eligible to receive PrEP. They also require to be well-trained on what procedures to follow when they initiate and follow up people on PrEP. The Kenyan

guidelines stipulate that PrEP can only be prescribed by a health care provider who has received training on use of antiretrovirals as PrEP.[16]

As the program in Kenya begins and expands, training as many health providers as possible expeditiously is necessary to efficiently and rapidly scale up PrEP delivery among at risk populations and thereby realize the greatest impact of PrEP. In chapter 4, we present evaluation results of a novel on-site modular training approach. We assessed knowledge, determined monthly PrEP uptake for six months following the training intervention, evaluated the costs and conducted key informant interviews to explore acceptability. Out findings demonstrate that on-site modular training is an effective, acceptable and low-cost way to provide PrEP education for health workers in public health facilities.

Chapter 5: PrEP roll out in Africa: status and opportunity

Following guideline recommendations by the World Health Organization (WHO), many countries in Africa, the region with the largest HIV burden have begun PrEP implementation. In chapter 5, we summarize the status of PrEP implementation in Africa and early lessons learnt from implementation. We detail the high interest in PrEP services among persons at high risk for HIV and the need to understand PrEP continuation which has been lower than expected. We also highlight challenges to introducing PrEP and suggest innovative strategies that can be employed to expand PrEP delivery in order to meet those at highest HIV risk.

Summary

This dissertation details a feasible and sustainable PrEP delivery approach that facilitates rapid scale up of PrEP within public health settings in Kenya. Many PrEP programs in Africa have just begun and are expected to grow. Lessons generated from this work are applicable to many of these PrEP programs and can be incorporated by countries that are integrating their PrEP programs in HIV care programs.

Chapter 2: Integrating pre-exposure prophylaxis services into public HIV care clinics in Kenya: Results from a pragmatic stepped-wedge randomized trial

Citation: Irungu, E. M., Mugwanya, K., Mugo, N., Bukusi, E., Donnell, D, Odoyo, J., Wamoni, E., Peacock, S, Morton, J., Ngure, K., Mugambi, M., Mukui, I., O'Malley, G. and Baeten, J. M. Integrating oral preexposure prophylaxis services into public HIV care clinics in Kenya: Results form a pragmatic stepped-wedge randomized trial. Lancet Glob Health *(under review)*.

INTEGRATING PRE-EXPOSURE PROPHYLAXIS SERVICES INTO PUBLIC HIV CARE CLINICS IN KENYA: RESULTS FROM A PRAGMATIC STEPPED-WEDGE RANDOMIZED TRIAL

Elizabeth M. Irungu[1,4], Kenneth K. Mugwanya[1], Nelly R. Mugo[1,5,] Elizabeth A. Bukusi[1,6], Deborah Donnell[1,7], Josephine Odoyo[6], Elizabeth Wamoni[5], Sue Peacock[1], Jennifer F. Morton[1], Kenneth Ngure[1,4], Mary Mugambi[8], Irene Mukui[8], Gabrielle O' Malley[1], Jared M. Baeten[1,2,3], for the Partners Scale-Up Project Team

Affiliations:

[1]Departments of Global Health, [2]Epidemiology, [3]Medicine, University of Washington, [4]School of Public Health, Jomo Kenyatta University of Agriculture and Technology, [5]Centre for Clinical Research, Kenya Medical Research Institute, [6]Centre for Microbiology Research, Kenya Medical Research Institute, [7]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, [8]National AIDS and STI Control Program

Corresponding author:

Elizabeth M. Irungu
P. O. Box 104018-00101
Nairobi, Kenya
Tel: +2546722561
Email: eirungu@uw.edu

Key words:

PrEP implementation; HIV care clinics; HIV serodiscordant couples; PrEP initiation; PrEP continuation

ABSTRACT

Background

Successful and sustainable models for HIV pre-exposure prophylaxis (PrEP) delivery in public health systems in Africa are needed.

Methods

Between January 2017 and December 2019, as part of Kenya's national public sector PrEP roll-out, we conducted a stepped-wedge cluster-randomized pragmatic trial to catalyze scale-up of PrEP delivery integrated in 25 public HIV care clinics. We conducted standardized case-based training of clinic staff, provided ongoing technical support, and abstracted data from client records. All PrEP provision was done by clinic staff without additional financial support.

Findings

A total of 4898 individuals initiated PrEP. The mean monthly PrEP initiations per clinic increased significantly from 0.1 (standard deviation [SD] 0.5) prior to 7.5 (SD 2.7) after intervention introduction (RR 23.7, 95% CI 14.2, 39.5, p<0.001). Of those initiating, 2640 (54%) were women, the median age was 31 (interquartile range [IQR] 25-39) years, and 4092 (84%) reported a partner living with HIV. Excluding individuals known to have intentionally discontinued PrEP (e.g., after antiretroviral therapy initiation by their partner), return for PrEP refill among individuals expected to return was 74% (2806/3789), 68% (2135/3136) and 62% (1661/2671) at 1, 3 and 6 months, and approximately 12% of those who missed a refill returned later for PrEP re-initiation. Tenofovir diphosphate was detected in 96% (68/71) of blood samples collected from a randomly-selected subset of clients. Six HIV infections were observed over 2531 person-years of observation (incidence 0.24 per 100 person-years), three of which occurred at the first visit after PrEP initiation.

Interpretation

In Kenya's large programmatic delivery of PrEP in HIV care clinics, we observed high uptake, reasonable continuation with high adherence, frequent PrEP restarts, and low

HIV incidence. Integration of PrEP services within public HIV care clinics in Africa is feasible.

Funding

NIMH (grant R01MH095507) and BMGF (grant OPP10556051).

Research in context:

Evidence before this study

Daily pre-exposure prophylaxis with oral TDF/FTC is a highly effective HIV prevention intervention. Delivery of PrEP at scale to people at substantial risk for HIV infection is necessary in order to attain maximal public health impact. Successful models of PrEP delivery have been described in high-income countries; however, there are few data that describe sustainable approaches for delivery of PrEP for HIV prevention for low- and middle-income settings.

Added value of this study

We conducted a real-world PrEP implementation program in which PrEP services were integrated into public HIV care clinics in Kenya. We demonstrate that by improving the capacity of health providers in those care clinics to offer PrEP services through training and technical support, PrEP uptake increased more than 20-fold and was sustained. With existing personnel and infrastructure, the high-volume HIV care clinics efficiently reached partners of HIV infected persons and other populations at HIV risk. PrEP users had reasonable continuation rates and objective evidence of high adherence. Restarting PrEP was common.

Implications of all the available evidence

We demonstrate that provision of PrEP services integrated in public HIV care clinics in Africa is feasible. Our findings inform Kenya's national scale up of PrEP and other countries in the African region that are considering implementation of national PrEP programs.

Introduction

Of the estimated 1.7 million new HIV infections that occurred in 2019, 60% occurred in the African region.[1] Pre-exposure prophylaxis (PrEP) against HIV has potential to reduce HIV incidence among populations at risk of HIV if able to be delivered with sufficient coverage.[36] In 2015, the World Health Organization recommended using daily oral tenofovir disoproxil fumarate (TDF), in combination with emtricitabine (FTC/TDF), as a safe and effective oral PrEP for persons globally at risk of HIV infection.[14] Many African countries have now developed policies that incorporate PrEP in their HIV prevention strategies.[13,17]

There are now extensive data from high-income countries describing diverse settings in which PrEP services are offered, including in clinics treating sexually transmitted infections, community-based organizations, commercial pharmacies, and by primary care and specialty providers.[37,38] In contrast, data describing PrEP scale-up models in low and middle income countries are limited. In many African countries, public HIV care and treatment programs have been very successful at scaling up antiretroviral therapy (ART) over the last 15 years and are an attractive choice for integration of PrEP delivery.[39] HIV care clinics in Africa routinely provide HIV prevention services including HIV testing services and condom distribution to uninfected partners of persons living with HIV, thus providing a ready PrEP-eligible population.[39,40] In addition, health providers in these clinics are conversant with prescribing and counselling on antiretroviral medication use, and the clinics have an established commodity management system for antiretrovirals and HIV test kits.

In 2017, Kenya launched a national commitment to PrEP as part of the HIV combination prevention strategy, focusing on holistic integration of PrEP services delivery within the public health system.[15,16] Data from clinical trials and demonstration projects of PrEP conducted in Kenya proved critical for regulatory approval and normative guidance formation related to PrEP, and thus the country was well-positioned to advance PrEP services early in Africa.[3,8] To provide real-world evidence of PrEP implementation in public HIV clinics in Kenya, and within Kenya's national PrEP program, we conducted an implementation trial of PrEP service delivery in 25 HIV care clinics.

Study Design

The Partners Scale-Up Project (ClinicalTrials.gov: NCT03052010) was a prospective pragmatic implementation evaluation of PrEP delivery integrated in 25 public HIV care clinics.[21] A stepped-wedge cluster randomized trial design, with each clinic as a cluster, was applied for this evaluation, taking into account a staggered approach because the intervention could not be implemented simultaneously in all clinics. The intervention consisted of PrEP training for health workers and provision of ongoing PrEP technical assistance to HIV clinics. The first month of the study (January 2017) constituted a baseline period, during which no intervention activities were implemented at any health facility. Subsequently at monthly intervals, beginning February 2017, 2-6 clinics HIV care clinics crossed over from control to intervention. By August 2017, all clinics were implementing the intervention (Figure 2) and follow-up continued through December 2019. The primary outcome was number of PrEP initiations comparing control and

intervention periods and additional outcomes included continuation, adherence, and fidelity to the PrEP program.

Study setting

Kenya has a generalized HIV epidemic with 4.9% of the adult population living with HIV and an estimated 36,000 new infections annually.[41] The majority of persons living with HIV in the country receive care and treatment services from public HIV care clinics. At these clinics, clients are encouraged to bring their partners for HIV testing, therefore providing a population that would benefit from PrEP should they test HIV negative.[42] Staffing at the clinics typically incudes clinical officers, nurses, pharmaceutical technologists, laboratory technicians, data clerks, HIV testing service providers and lay health workers.[19] In consultation with the Kenyan National AIDS and STI Control Program (NASCOP) and county-level health officials, 24 high volume public health HIV care clinics were identified in western (former Nyanza province) and central (including former Central and Nairobi provinces) regions, areas with medium to high HIV incidence.[43] All 24 identified clinics were invited and agreed to participate in the project, and one clinic later added on a satellite clinic. We used the main 24 clinics for evaluation of the primary outcome, but included the 25th clinic in the other analyses.

Intervention

Health Provider Training

Health providers from the selected HIV care facilities received a two-day hotel-based interactive PrEP training using a curriculum developed by the Kenya Ministry of Health

in collaboration with implementing partners, including the study team.[17] The training sessions included introduction to PrEP, risk assessment and indications for PrEP, procedures at initiation and follow up visits and documentation of visits. The training had didactic sessions, discussions of case studies, role plays and practical exercises. Pre- and post-training assessments were done to assess PrEP knowledge.[44]

Health providers began providing PrEP services including demand creation, risk assessment, prescribing, counseling, and retention activities within a month after training. Clinic staff were not employed by the project and no additional staffing or financial support was provided to the clinics; thus, services were provided without altering the existing infrastructure. All PrEP medication and HIV test kits were provided by the Kenya Ministry of Health.

Provision of Technical Assistance

Project staff who had previously developed expertise in PrEP research and clinical delivery, served as technical advisors, mentoring health providers in participating clinics in PrEP delivery following the standardized PrEP training. Technical advisors were nurses and clinical officers employed by the study, and they also led the health provider trainings. Each technical advisor provided support for up to four clinics. Technical assistance activities involved supporting providers to do demand creation activities by modelling health talks at facility waiting bays, and real-time consultation, e.g., when providers needed clarity on determination of eligibility and how to complete various Ministry of Health clinical, pharmacy, or monitoring and evaluation tools. They also

identified and addressed training gaps, facilitated continuous medical education and on-job-training sessions. They visited clinics at least twice a month in the first year and monthly or less frequently thereafter as facilities became comfortable with PrEP delivery. Observations made during technical assistance visits were detailed in structured reports. Technical advisors met weekly as a group to discuss observations made across facilities and best practices were shared across clinics.

PrEP delivery

Kenya normative guidelines recommend PrEP for HIV uninfected individuals who report multiple sex partners, a history of a recent sexually transmitted infection, no or inconsistent condom use, engagement in transactional sex, recurrent use of post-exposure prophylaxis, recreational drug use, or having partners living with HIV who are not virally suppressed. In 2017, Kenya committed that PrEP would be available at public health facilities nationwide.[15]

PrEP services were provided according to Kenya Ministry of Health guidelines.[15] Those guidelines recommend behavioral risk assessments and clinical review prior to issuing PrEP prescriptions. While serum creatinine testing at baseline is recommended, lack of testing should not delay PrEP initiation. PrEP users should attend clinical visits one month after initiation and quarterly thereafter while PrEP need is ongoing; at those visits, medication side effects and medication adherence via self-report are determined. PrEP is discontinued for individuals testing HIV seropositive.

At most clinics, providers elected to contact clients with missed appointments (similar to standard practice for clients living with HIV receiving antiretroviral therapy) and issue

new appointments if there was interest in continuing PrEP services. Health providers documented when PrEP users were not expected to return for refill visits – e.g., when PrEP users reported they no longer wanted PrEP. Individuals who failed to attend a visit and could not be contacted were considered not expected to attend the next scheduled visit.

Randomization and masking

Clinics were stratified by region and then randomized to the order in which they would start receiving the intervention. At two stakeholder events attended by county health officials and facility leadership (one in the western region and another in the central region), facility staff picked out numbered opaque balls which represented the position of the clinic in the order of project implementation. There was no masking for this study.

Data Abstraction

Kenya Ministry of Health standard clinic encounter form records of individuals receiving PrEP services were abstracted by trained project staff using SurveyCTO® platform onto a central database. Records included demographic information, behavior risk assessment evaluation, medical assessment and STI evaluation, laboratory test requests and results, details of PrEP dispensing and adherence assessment (Supplementary material). Only data from persons aged 18 years and older were abstracted.

Statistical power:

We estimated power for the primary endpoint of PrEP initiations. Using 24 clinics with a baseline period, two to four clinics implementing at each step, and 50 at-risk HIV-

uninfected persons initiating PrEP per clinic every 6 months (4800 individuals in total) we would have > 90% power to detect a minimum 10% difference in the number of at-risk HIV-uninfected individuals initiating PrEP.[21]

Data analysis

The primary outcome for this evaluation was the number of people initiating PrEP per clinic per month comparing intervention to control periods. Other outcomes included the number of people continuing to use PrEP, adherence to PrEP, incident HIV infections, and fidelity to core components of PrEP delivery. PrEP initiation was defined as documentation of having received a PrEP prescription in facility records. Visit dates and windows (the period between 15 days before the expected visit date to 15 days before the next expected visit date) were determined for all persons initiating PrEP based on the initiation date. PrEP continuation was defined as the proportion of people expected to come for a visit who had a documented PrEP refill within the visit window. Core components of PrEP delivery that were evaluated were HIV risk assessment, HIV testing and acute HIV infection assessment prior to PrEP initiation, serum creatinine testing at baseline, and PrEP prescription and dispensing. We determined the proportion of visits in which these activities were documented as completed.

As an objective assessment of adherence, whole blood samples were obtained from individuals returning for PrEP refill visits at randomly-selected clinics on a random subset of days in a month. The blood was transported to centralized project sites where dried blood spots (DBS) were prepared. Intracellular tenofovir diphosphate

concentrations were determined from the dried blood spots using validated liquid chromatography-tandem spectrometry.[45,46]

Descriptive analyses of demographic, HIV risk and fertility characteristics of people initiating PrEP were performed. For those reporting sex partners living with HIV, HIV risk was summarized based on an empiric risk score developed to quantify HIV risk among HIV serodiscordant couples.[47] Characteristics assessed to calculate the score included age of the HIV uninfected partner, number of children within the partnership, circumcision status of HIV uninfected men, whether the couple was cohabiting and having unprotected sex in the month prior to starting PrEP. In previous studies of HIV serodiscordant couples a score ≥3 was associated with a HIV incidence greater than 3% per year.[47] We conducted a cluster-level analysis to determine change in number of people initiating PrEP per clinic per month between intervention and control periods using a negative binomial mixed effects model with log link. The model also included step, clinic volume and region as fixed effects and a random effect for each clinic. To determine whether number of monthly PrEP initiations per clinic changed over time after intervention implementation, we conducted an analysis restricted to the intervention period using a negative binomial mixed effects model with log link. The model included duration since start of PrEP implementation in years as the primary exposure, region, clinic volume and calendar time as fixed effects and a random effect for each clinic.

We present proportions of expected PrEP users who had PrEP refills at 1, 3, 6 and 12 months post PrEP initiation. We determined the proportion of randomly obtained DBS

that have tenofovir diphosphate detected and proportion of all initiation visits in which core components of PrEP service delivery were completed.

To estimate the potential impact of PrEP availability on incident HIV, we compared the number of observed new HIV infections to an expected HIV incidence estimated using a simulated counterfactual model using data from the placebo arm of the Partners PrEP Study, a clinical trial conducted among HIV serodiscordant couples in Kenya and Uganda.[3] Comparisons were limited to individuals reporting a sex partner known to be living with HIV and to follow-up within the first year of starting PrEP. The comparison limited to serodifferent partnerships potentially reduces temporal trends in HIV transmission risk in communities, as the principal risk of HIV is from within the partnership.[8] We constructed 10,000 bootstrap samples of 4092 couples each with a distribution of sex and HIV risk scores to match the population in the Partners Scale-Up Project.[47] The number of HIV seroconversions was predicted for each bootstrap sample and the counterfactual population incidence determined as the mean number of HIV seroconversions across the 10,000 samples. The 95% confidence interval was the number of seroconversions from the 250th & 9750th datasets after sorting by number of seroconversions. HIV incidence for the counterfactual population was computed by dividing the mean number of seroconversions by the mean follow up time from 10,000 bootstrap samples. The incidence rate ratio was computed by comparing observed HIV incidence in this study to the computed counterfactual estimate and the 95% confidence interval was calculated using a Poisson distribution. Sensitivity analyses were also conducted, with follow up limited to 6 months after starting PrEP.

Analyses were conducted using R software 3.5.2 and Stata version 15 (StataCorp, College Station, TX).

Ethics

This program implementation evaluation protocol was approved by the scientific and ethics review unit of the Kenya Medical Research Institute and the University of Washington Human Subjects Division enabling analysis of de-identified and delinked programmatic data. Thus, individual consent was not required. Persons who participated in random blood draws for tenofovir diphosphate detection provided written informed consent.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Intervention effect

Between January 2017 and June 2019, 4898 persons initiated PrEP in the 25 public HIV clinics: 27 during the control period and 4871 in the period post intervention (Figure 3). The mean monthly number of PrEP initiations per clinic prior to intervention implementation was 0.1 (standard deviation [SD] 0.5) and 7.5 (SD 2.7) after implementation (rate ratio [RR] 23.7, 95% confidence interval [CI] 14.2, 39.5, $p < 0.001$).

PrEP initiations were relatively stable: each additional year after intervention implementation was associated 0.95-fold (95% CI 0.80, 1.13, p=0.5) reduction in number of clients initiating PrEP per clinic per month, a change that was not statistically significant.

Characteristics of persons starting PrEP

The median (interquartile range [IQR]) age of those initiating PrEP was 31 (25-39) years and 2640 (54%) were female (Table 1). The majority (4092 [84%]) reported having a sex partner living with HIV and they had known their HIV serodiscordant status for a median 1 (0.2, 4.5) year prior to starting PrEP. Seventy percent (2845/4092) of those in serodiscordant partnerships had a risk score of 3 and above, associated with an anticipated HIV incidence greater than 3%. Besides having a partner living with HIV, individuals initiating PrEP reported other HIV risk behavior that made them eligible for PrEP initiation including inconsistent or no condom use 2817 (58%), not knowing the HIV status of their partners 789 (16%), and having sex with multiple partners 565 (12%).

There were 167 (11%) and 262 (16%) women who were pregnant or breastfeeding a child, respectively, at the time of PrEP initiation. Among women with available data, about half (53%) reported using contraception and 21% had immediate desire for fertility.

PrEP continuation and adherence

Of the 4898 people who initiated PrEP, 57%, 44%, 34% and 23% returned for refill visits at 1,3,6, and 12 months post PrEP initiation. However, frequently there was

documentation that individuals were no longer expected to return for PrEP. Overall, there were 4025 reasons documented for PrEP users who were not expected to attend PrEP refill visits. Unsuccessful attempts to contact PrEP users made up the majority of documented reasons (3388 [84%]), Among those successfully contacted, reasons why PrEP users were not expected included reduced HIV risk (56%) due to HIV positive partner viral suppression, decision to use condoms consistently, realization of conception (and subsequent consistent condom use), relocation away from clinic area (25%), experience of side effects (5%) and other reasons including pill burden and being busy (14%).

Excluding individuals known to have discontinued PrEP, the proportion expected to return for visits was 77% at month 1, 64% at month 3, 54% at month 6 and 39% at month 12. Of those expected 74%, 68%, 62% and 60% attended their refill visits at 1, 3, 6 and 12 months post PrEP initiation. At all quarterly visits, 12% of clients who had failed to attend the prior refill visit returned for PrEP medication (i.e., effectively restarting PrEP) (Figure 4).

A total of 3028 individuals (62% of those starting PrEP) had at least one refill visit within the first three months of PrEP initiation. Women (odds ratio [OR] 1.15, 95% CI 1.03,1.29), individuals aged > 24 years (OR 1.48, 95% CI 1.28, 1.70), those reporting a partner living with HIV (OR 2.44, 95% CI 2.09, 2.84), and women with immediate fertility desires (OR 1.94, 95% CI 1.44, 2.62) were more likely to have at least one refill visit in the three months after PrEP initiation. In addition, among individuals having a sex

partner living with HIV, those with an HIV risk score of 3 or greater were more likely to have a visit within three months of PrEP initiation (OR 1.17, 95% CI 1.02, 1.34) (Table 1).

Over the course of the study, clients self-reported good adherence to PrEP at 70% (10643/15219) of follow up visits. Seventy-one dried blood spots were collected and tested and tenofovir–diphosphate was detectable in 68 (96%) samples.

HIV incidence

A total of 2531 person-years of follow up were accrued with a mean follow up 6.3 (SD 8.1) months. Six individuals (5 female and 1 male) initiating PrEP tested HIV positive during the project period, translating to a HIV incidence of 0.24 per 100 person-years. All seroconversions occurred within the first year and three of these individuals tested HIV positive at the first visit after PrEP initiation. For persons reporting sex partners living with HIV, HIV incidence during the first year of PrEP use was 0.42 per 100 person years (6 events in 1423 person-years). This incidence represents a 90% (95% CI 76%, 95%) reduction compared to a predicted incidence of 4.05 (95% CI 3.4, 4.7) per 100 person-years that would be expected for HIV serodifferent partners with similar sex and risk characteristics in the absence of PrEP and ART. Sensitivity analyses comparing predicted to observed HIV incidence at six months of PrEP use did not yield substantially different results (3.79 [95% CI 2.7, 5.0] vs 0.65 [95% CI 0.24, 1.43]).

Fidelity to PrEP guidelines

At PrEP initiation, HIV risk assessment was documented for all individuals. HIV testing, acute HIV assessment and PrEP dispensing was documented to have been done at

99.8%, 99.5% and 99.5% of initiation visits. Assessment of sexually transmitted infections was done at 87% of visits. Over the entire project period, 138 (2.8%) of clients had a creatinine test result recorded: 61 at baseline and 77 during PrEP follow-up.

Discussion

In this large-scale evaluation of PrEP delivery in Kenya, we observed sustained high monthly uptake of PrEP, demonstrating that public HIV care clinics are a feasible delivery setting for integrating PrEP services. The clinics, which attend to hundreds of HIV infected persons every month, comfortably added an average of seven PrEP initiations per month per clinic, with high fidelity and utilizing their existing infrastructure and workforce. It is interesting to note that while the majority of individuals initiating PrEP in these clinics reported having a sex partner known to have HIV, almost one in five did not. There was high adherence among those who continued to take PrEP, with almost all tested samples having evidence of TDF/FTC use.

We observed that individuals discontinued PrEP use over time, and for many individuals PrEP use may have been aligned to HIV risk, a concept described as 'prevention-effective adherence.[48] Persons with HIV risk scores associated with greater risk of HIV infection at baseline were more likely to continue using PrEP for greater than three months. Additionally, among those who provided reasons for discontinuation, over 50% were related to perception of reduced HIV risk, including viral suppression of their partners living with HIV who had initiated antiretroviral therapy or decisions to use condoms consistently. Use of PrEP is not expected to be life-long and individuals are encouraged to discontinue when they are no longer at risk.[49,50] For HIV serodiscordant

couples, use of PrEP in a time-limited fashion prior to and for the first months of antiretroviral treatment (i.e., as a bridge to viral suppression) is recommended by evidence-supportive normative guidance.[8]

Notably, about 12% of persons who had failed to attend a refill visit showed up for a refill at the next visit, suggesting that individuals continued to think about and assess their HIV risk and resumed PrEP when they need to. Similar reports of PrEP restarts were reported in other PrEP settings.[51] Since most people will not inform health providers of their intent to discontinue PrEP, a receptive attitude by providers in HIV care clinics to individuals who have previously discontinued PrEP use or have had missed refill visits will likely encourage PrEP restarts, as has been observed in HIV treatment programs.[52,53] In addition, clinics should strive to address barriers that may keep clients from returning for services such as long waiting times that would be a deterrent for those with busy schedules.

As PrEP is a biomedical intervention, increasing the capacity of health providers to offer PrEP services is critical. Training health providers and providing technical support during implementation was associated with increased PrEP service delivery in participating clinics. To achieve rapid scale up of PrEP services in the country it is crucial that efficient, cost-effective training modalities and innovative means of providing technical assistance are employed. These will ensure that health providers in public health facilities acquire knowledge about PrEP and feel confident in their ability to offer services.[44,54]

There are strengths to this study. First, we conducted the study in 25 high volume public HIV care clinics distributed in various geographical areas within central and western Kenya, increasing the generalizability of our findings. Second, use of the stepped-wedge study design enabled us to rigorously evaluate the impact of our intervention within the national programmatic scale up of PrEP. There are several limitations to our study. First, for many who did not continue using PrEP clinic documentation did not demonstrate a reason and HIV status after discontinuation was not determined. Second, our analysis utilized programmatic data abstracted from client records which often has problems of completeness.[55] Finally, we used a counterfactual simulation model to compare HIV incidence in this project to that anticipated in the absence of PrEP and ART, and like all non-contemporaneous comparisons, this counterfactual could be subject to bias. Of note, although secular changes in HIV transmission risk may have occurred, the main HIV transmission risk stems from within the HIV serodiscordant partnership, mitigating some risk of bias in this approach.

Conclusion

In this study of PrEP delivery integrated in public HIV care clinics in Kenya, PrEP uptake was high, continuation was reasonable, and those who continued to attend clinics had high adherence and low rates of HIV acquisition. Integration of PrEP in public health facilities is feasible and can be done with high fidelity when health providers are trained and receive technical support related to PrEP service delivery. Evidence from this work will inform other countries in the region that are considering implementation of national PrEP programs.

Data sharing

The study protocol, statistical plan and data from the Partners Scale-Up Project are available by contacting the International Clinical Research Center at the University of Washington (icrc@uw.edu).

Acknowledgements

The study was funded by the National Institute of Mental Health of the US National Institutes of Health (grant R01MH095507) and the Bill & Melinda Gates Foundation (grant OPP10556051).

Table 1: Baseline demographic characteristics and HIV risk behavior of individuals initiating PrEP and predictors of having at least one refill visit in the first three months

	All participants (N=4898) n (%)	Participants with at least 1 visit within 3 months of PrEP start (N=3028) n (%)	OR (95%CI)
Demographics			
Sex			
Male	2257 (46%)	1355 (60.0%)	
Female	2640 (54%)	1672 (63.3%)	1.15 (1.03 – 1.29)
Age, years			
18-24	969 (20%)	526 (54.3%)	
25-34	2118 (43%)	1304 (61.6%)	1.35 (1.16 – 1.57)**
>35	1811 (37%)	1198 (66.2%)	1.65 (1.40 – 1.93)**
Marital status			
Single	347 (7%)	137 (39.5%)	
Married/Cohabitating	4466 (91%)	2843 (63.7%)	2.67 (2.15 – 3.35)**
Widowed/Separated	85 (2%)	48 (56.5%)	1.99 (1.23 – 3.21)**
Reported HIV Risk Behavior			
Has HIV positive partner	4092 (84%)	2676 (65.4%)	2.44 (2.09 – 2.84)**
Inconsistent or no condom use	2817 (58%)	1741 (61.8%)	1.00 (0.89 – 1.12)
Unknown status of sex partner	789 (16%)	379 (48.0%)	0.51 (0.44 – 0.59)**
Multiple partners	565 (12%)	267 (47.3%)	0.51 (0.43 – 0.61)**
Recurrent sex under the influence of alcohol	111 (2%)	54 (48.7%)	0.58 (0.40 – 0.84)**
Engaging in transactional sex	67 (1%)	26 (38.8 %)	0.38 (0.24 – 0.63)**
Recurrent PEP use	55 (1%)	31 (56.4%)	0.80 (0.47 – 1.36)
Recent sexually transmitted infection	44 (1%)	27 (61.4%)	0.98 (0.53 – 1.80)
Ongoing intimate partner/gender-based violence	35 (1%)	17 (48.6%)	0.58 (0.30 – 1.12)

Injection drug use	5 (0%)	5 (100%)	-
Not circumcised (men only)*	385 (19%)	237 (61.6%)	0.99 (0.82- 1.20)
Characteristics, HIV serodiscordant couples			
Number of children with partner*			
0	888 (36%)	618 (69.6%)	
1-2	957 (38%)	653 (68.2%)	0.94 (0.77 – 1.14)
3 or more	657 (26%)	469 (71.4%)	1.09 (0.87 – 1.36)
Time known to be discordant, years			
< 1 year	1093 (44%)	743 (68.0%)	
1-3 years	613 (25%)	432 (70.5%)	1.12 (0.91 – 1.39)
>3 years	760 (31%)	538 (70.8%)	1.14 (0.93 – 1.40)
HIV risk score**			
0-2	1247 (31%)	785 (63.0%)	
3-5	2351 (58%)	1556 (66.2%)	1.15 (1.00 – 1.33)
6-9	494 (12%)	335 (67.8%)	1.24 (0.99 – 1.57)
Pregnancy and Fertility			
Pregnant*	167 (11%)	114 (68.3%)	1.26 (0.90 – 1.78)
Breastfeeding*	262 (16%)	163 (62.2%)	0.89 (0.68 – 1.17)
Using contraception*	968 (53%)	633 (65.4%)	0.90 (0.74 – 1.09)
Fertility Desires			
No fertility desires	648 (43%)	400 (61.7%)	
Immediate	318 (21%)	241 (75.8%)	1.94 (1.44 – 2.62)**
Future	479 (32%)	309 (64.5%)	1.13 (0.88 – 1.44)
Don't know	65 (4%)	40 (61.5%)	0.99 (0.59 – 1.68)

*There are missing data for various variables as follows: male circumcision 292 (13%), number of children with partner 1590 (39%), time known to be HIV discordant 1624 (40%), pregnancy 1154 (44%), breastfeeding 771 (31%), contraception 820(31%), fertility desires 1130 (43%).

** Statistically significant at $P < 0.05$

Figure 2: Order of implementation across clinics

Clinic	Start Date	Assigned Start Month	Jan, 2017	Feb, 2017	Mar, 2017	Apr, 2017	May, 2017	Jun, 2017	Jul, 2017	Aug, 2017	Sep, 2017 - Jun, 2019
25	3-Aug-17	Aug, 2017	C	C	C	C	C	C	C	I	I
24	3-Aug-17	Aug, 2017	C	C	C	C	C	C	C	I	I
23	27-Jul-17	Aug, 2017	C	C	C	C	C	C	C	I	I
22	17-Jul-17	Jul, 2017	C	C	C	C	C	C	I	I	I
21	10-Jul-17	Jul, 2017	C	C	C	C	C	C	I	I	I
20	10-Jul-17	Jul, 2017	C	C	C	C	C	C	I	I	I
19	30-Jun-17	Jul, 2017	C	C	C	C	C	C	I	I	I
18	14-Jun-17	Jun, 2017	C	C	C	C	C	I	I	I	I
17	25-May-17	Jun, 2017	C	C	C	C	C	I	I	I	I
16	25-May-17	Jun, 2017	C	C	C	C	C	I	I	I	I
15	25-May-17	Jun, 2017	C	C	C	C	C	I	I	I	I
14	25-May-17	Jun, 2017	C	C	C	C	C	I	I	I	I
13	19-May-17	May, 2017	C	C	C	C	I	I	I	I	I
12	2-May-17	May, 2017	C	C	C	C	I	I	I	I	I
11	2-May-17	May, 2017	C	C	C	C	I	I	I	I	I
10	18-Apr-17	Apr, 2017	C	C	C	I	I	I	I	I	I
9	4-Apr-17	Apr, 2017	C	C	C	I	I	I	I	I	I
8	4-Apr-17	Apr, 2017	C	C	C	I	I	I	I	I	I
7	4-Apr-17	Apr, 2017	C	C	C	I	I	I	I	I	I
6	4-Apr-17	Apr, 2017	C	C	C	I	I	I	I	I	I
5	4-Apr-17	Apr, 2017	C	C	C	I	I	I	I	I	I
4	3-Mar-17	Mar, 2017	C	C	I	I	I	I	I	I	I
3	3-Mar-17	Mar, 2017	C	C	I	I	I	I	I	I	I
2	7-Feb-17	Feb, 2017	C	I	I	I	I	I	I	I	I
1	7-Feb-17	Feb, 2017	C	I	I	I	I	I	I	I	I

C – Control period, I – Intervention period

Figure 3: Cumulative number of PrEP initiations

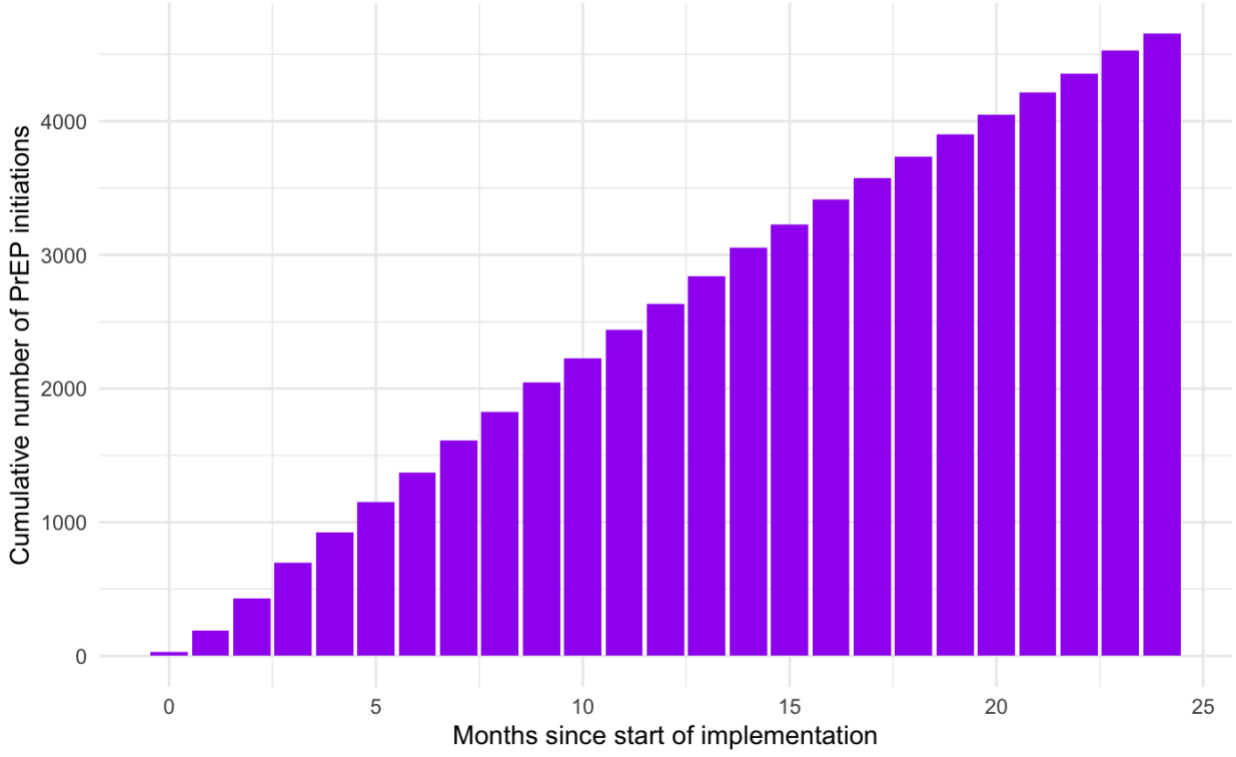


Figure 4: PrEP continuation

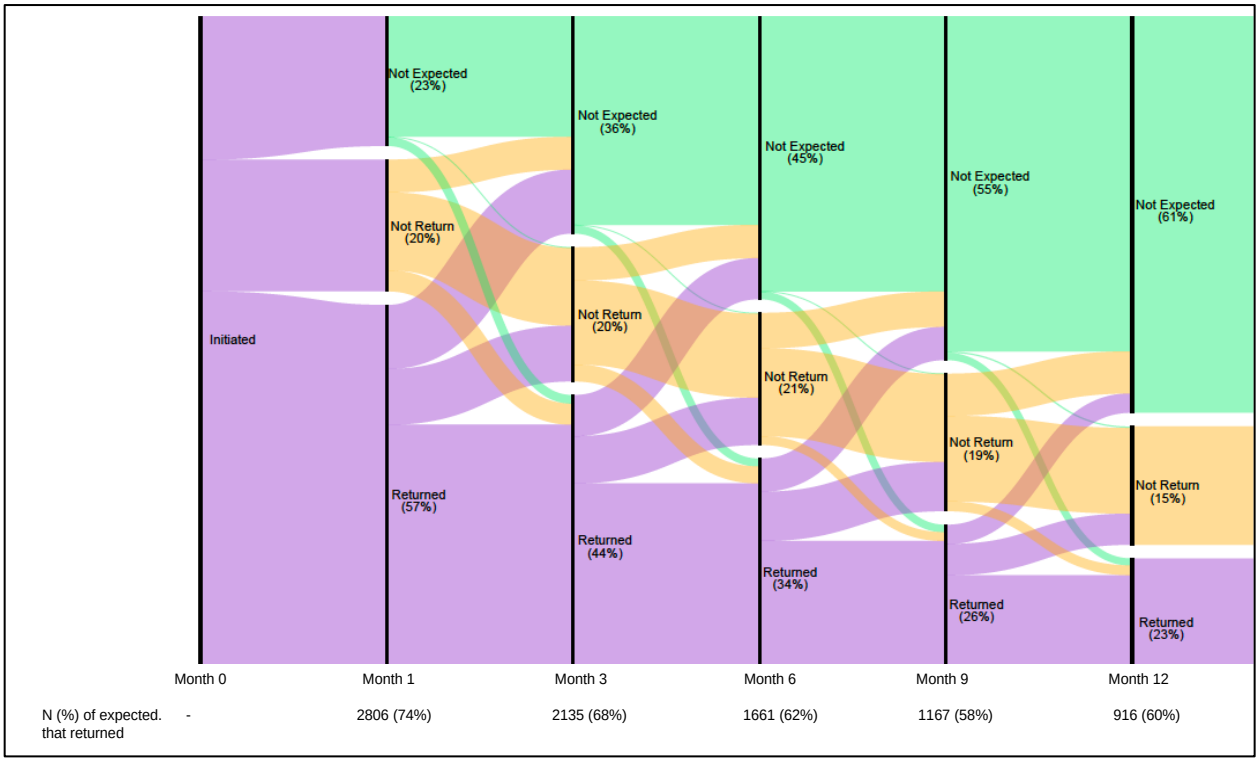


Figure 4 illustrates proportion of PrEP users returning (purple), not returning (orange) and not expected (green) for refill visits, by month. It also illustrates individuals with missed prior visits returning for PrEP refills. The table beneath the plot details the number and proportion of those expected who returned for PrEP refills, by visit month.

Chapter 3: Process evaluation of PrEP implementation in Kenya: Adaptation of practices and contextual modifications in public HIV care clinics

Citation: Irungu, E. M., Ngure, K., Mugwanya, K., Dolla, A., Ongolly, F., Mugo, N., Bukusi, E., Odoyo, J., Wamoni, E., Morton, J., Baeten, J. M. and O'Malley, G. Process evaluation of PrEP implementation in Kenya: Adaptation of guidelines and cotextual modifications in public HIV care clinics. J Int AIDS Soc (*under review*).

PROCESS EVALUATION OF PrEP IMPLEMENTATION IN KENYA: ADAPTATION OF PRACTICES AND CONTEXTUAL MODIFICATIONS IN PUBLIC HIV CARE CLINICS

Elizabeth M. Irungu[1,5], Josephine Odoyo[6], Elizabeth Wamoni[7], Elizabeth A. Bukusi[1,4,6], Nelly R. Mugo[1,7], Kenneth Ngure[1,5], Jennifer F. Morton[1], Kenneth K. Mugwanya[1], Jared M. Baeten[1,2,3]*, Gabrielle O' Malley[1] for the Partners Scale-Up Project Team

Affiliations:

[1]Departments of Global Health, [2]Epidemiology, [3]Medicine, [4]Obstetrics and Gynecology, University of Washington, Seattle, USA

[5]School of Public Health, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

[6]Centre for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya

[7]Centre for Clinical Research, Kenya Medical Research Institute, Nairobi, Kenya

*Present affiliation: Gilead Sciences, Foster City, USA

Corresponding author:

Elizabeth M. Irungu

P. O. Box 104018-00101

Nairobi, Kenya

Tel: +2546722561

Email: eirungu@uw.edu

Key words:

PrEP implementation; adaptation, public HIV care clinics; PrEP initiation; PrEP continuation

ABSTRACT

Background

In Africa, oral pre-exposure prophylaxis (PrEP) is largely provided via over-burdened public health HIV care clinics. Successfully incorporating PrEP services into these clinics may require adaptations to practices outlined in national implementation guidelines and modifications to routine existing service delivery.

Methods

The Partners Scale-Up Project was a prospective implementation science evaluation that aimed to catalyze integration of PrEP in 25 public HIV care clinics in Kenya. Between May and December 2018, we conducted qualitative interviews with health providers and documented clinic observations in technical assistance (TA) reports to understand the process of PrEP service integration and scale-up. We analyzed 36 health provider interviews and 25 TA reports to identify clinic level adaptations to activities outlined in Kenyan Ministry of Health PrEP guidelines and modifications made to existing service delivery practices to successfully incorporate PrEP services. Identified adaptations were reported using the expanded framework for reporting adaptations and modifications (FRAME).

Results

All clinics (n=25) performed HIV testing, HIV risk assessment, PrEP education and adherence counselling as stipulated in the guidelines. Most clinics initiated clients on PrEP without creatinine testing if otherwise healthy. While monthly refill appointments are recommended, majority of clinics issued PrEP users 2-3 months of pills at a time, depending on client request and adherence. Clinics also implemented practices which had not been specified in the guidelines including incorporating PrEP-related topics into routine health talks, calling clients with missed PrEP appointments, discussing PrEP service delivery in regular staff meetings, “fast-tracking” PrEP clients, providing PrEP at non-regular clinic hours, and dispensing PrEP in clinic rooms rather than separately at

clinic-based pharmacies. PrEP initiation numbers were highest among clinics that did not require creatinine testing, conducted peer on-the-job PrEP training and those that discussed PrEP delivery in their routine meetings. Above-average continuation rates were observed among clinics that discussed PrEP in their routine meetings, dispensed PrEP in clinic rooms and offered PrEP at non-regular hours.

Conclusion

Health providers in public HIV care clinics instituted practices and made innovative adaptations to PrEP delivery to reduce barriers for clients and staff. Encouraging clinic level adaptations to national implementation guidelines will facilitate scale-up of PrEP delivery.

Clinical Trial Number: NCT03052010

Background

The World Health Organization issued a strong recommendation for use of oral pre-exposure prophylaxis (PrEP), a highly potent HIV prevention intervention that has the potential to reduce HIV incidence markedly if used effectively [2]. Many countries in Africa, the region disproportionately affected by HIV, have adopted this recommendation and begun implementing PrEP programs [1,14]. However, despite close to half of all global PrEP initiations being in Africa, scale up in the region remains sub-optimal [12,13].

Integrating PrEP services into existing programs may increase access for people at risk of HIV, while promoting the best use of available resources [56-58]. In theory, public HIV care clinics in Africa are an opportune venue for introduction and integration of PrEP services; clinic staff can identify uninfected partners of their clients living with HIV, have expertise in HIV testing and prescribing antiretroviral drugs and have established ART supply logistics [39]. However, these clinics are typically over-burdened, short-staffed, and have associated stigma, which may hinder PrEP implementation efforts. Mitigating these constraints may necessitate adapting activities detailed in guidelines and instituting modifications to routine practices in the clinics [27,59,60].

Moving evidence-based interventions (EBIs) from research settings to scaled implementation requires adaptations of the EBI to better fit within the contextual realities of those delivering the intervention, the needs of the local target population, or to respond to unanticipated challenges [61,62]. In addition, when EBIs are integrated into

existing programs which were developed to deliver other interventions, modifications to clinic service delivery practices will be necessary to make the new program fit. Unfortunately, the description of what and why modifications are made is infrequently documented and shared in peer reviewed literature, thus limiting the dissemination of learnings from real world settings [62]. Using the expanded framework for reporting adaptations and modifications (the FRAME), this paper describes adaptations made by public HIV care clinics in Kenya to integrate the delivery of PrEP with the intention of sharing lessons learned for others interested in scaling PrEP [31].

Context

In 2018, approximately 1.4 million adults were living with HIV and in the same year, an estimated 36,000 adults acquired HIV.[41] The majority of people living with HIV in Kenya receive HIV care services free of charge in public HIV care clinics [18,63,64]. The clinics are staffed by clinicians, nurses, pharmacy staff, laboratory technicians, counsellors and data clerks. In 2016, Kenya revised the national HIV care and treatment guidelines and recommended PrEP as an additional HIV prevention intervention for people at risk of acquiring HIV [15]. By July 2020, Kenya had one of the largest PrEP programs in Africa with more than 60,000 individuals having initiated PrEP [12,65].

Guidelines for PrEP delivery

According to national guidelines, individuals eligible to use PrEP are those who are HIV uninfected and who report having multiple sex partners, having sex partners living with HIV and not virally suppressed, have sex partners of unknown HIV status, have had a recent sexually transmitted infection, have no or inconsistent condom use, engage in

transactional sex, have recurrent use of post exposure prophylaxis or engage in recreational drug use [15]. At PrEP initiation visits, a behavioral risk assessment, risk reduction counselling and HIV testing should be performed. Clients should be evaluated to identify symptoms of acute HIV infection, sexually transmitted infections (STIs), and presence of known contraindications to PrEP medication before a prescription is issued. Creatinine testing is recommended at baseline, but absence of test results should not delay PrEP initiation. Clients should have a clinical review after 1 month of PrEP use and every 3 months thereafter with monthly refill visits in between. Quarterly follow up visits should include a rapid HIV test, an assessment of acute HIV symptoms, an evaluation of on-going need for PrEP, medication side effects and medication adherence. Initiation and follow up visits should be documented in a clinical encounter form (CEF).

Methods:

The Partners Scale-Up Project was a prospective, implementation study conducted in 25 high volume public HIV care clinics in western and central Kenya. The project aimed to catalyze integration of PrEP in these clinics using existing facility infrastructure and personnel capacity [21]. Beginning January 2017, health providers were trained on PrEP delivery by project staff, and clinics began delivering PrEP services shortly thereafter [44]. Project staff provided routine on-going technical assistance (TA) and mentorship to providers. This analysis is based on two data sources; summary TA reports and key informant interviews (KIIs).

At the end of each technical assistant visit, reports that detailed clinic observations and conversations with clinic staff were completed. The report template prompted a description of successes and challenges with demand creation, identification of PrEP clients, PrEP service delivery, workforce, commodities, and client retention (see Additional File 1). Approximately 1 year into the project, a summary TA report was generated for each clinic.

Between May and December 2018, we interviewed health care providers using semi-structured interview guides with probes to elicit detail on how PrEP services were integrated into routine clinic practice (see Additional File 2). We purposively sampled different cadres to capture different perspectives. Interviews were conducted in either English or Kiswahili depending on the interviewee's preference. Interviews were audio recorded, translated to English where necessary, and transcribed by the interviewer. Average interview duration was 45 minutes.

Interview transcripts and technical assistance summary reports were analyzed in Dedoose (Sociocultural Research Consultants LLC, Los Angeles, CA). An initial codebook was developed with codes based on the national PrEP delivery guidelines and investigator knowledge of clinical practices at the public HIV clinics. Additional codes were added inductively as initial transcripts were reviewed and coded. The first eight transcripts and six TA reports were dual coded by at least two members of the study team and differences in coding were discussed until consensus was reached. The

final codebook was applied to all transcripts by one member of the study team and reviewed by another.

In order to assess and quantify adherence to PrEP implementation guidelines, we created three categories: i) *implemented all the time* if all interviews and TA reports for a particular clinic indicate that the activity was implemented, ii) *implemented some of the time* if some interviews and TA reports for a particular clinic indicate that the activity was not always implemented, iii) *not implemented* if all interviews and TA reports for a particular clinic indicate that the activity was not implemented. In addition, we categorized clinics as having made modifications to their existing program practices if any of the interviews and TA reports of a particular clinic indicated that there had been a change at any time. The coded excerpts of text were reviewed, and the categories described above were applied.

We conducted descriptive analysis to determine the frequency with which clinics adhered to activities as stipulated in the guidelines and modified their routine practice. We also compared mean monthly PrEP initiations and continuation rates as of December 2018 between clinics making adaptations to PrEP guidelines and those instituting changes to routine HIV program practices compared to those that did not.

We used the FRAME, a refined framework, for reporting adaptations [31]. Elements of this framework include a description of what was adapted, the nature and timing of the adaptation, whether the adaptation was planned or not, who determined that the

adaptation should be made, for whom it was made, whether it was fidelity-consistent and the goals of the adaptation. Guided by this framework, we describe observed adaptations and report on elements that are relevant to our project. All adaptations were made after PrEP implementation had begun in clinics. We determined adaptations to be fidelity consistent if they did not remove core elements of PrEP delivery including HIV testing before PrEP initiation and quarterly thereafter, eligibility assessment and issuance of PrEP prescriptions and dispensing the medication. We present results in a tabular form. Finally, we used thematic content analysis to identify overarching motivations for adaptations and modifications.

Ethics statement

The Scientific and Ethics Review Unit of the Kenya Medical Research Institute and the Human Subjects Division of the University of Washington approved the study protocol. Written informed consent was provided by all interviewed participants.

Results

We interviewed 36 providers of whom 56% were female (Table 2). Their median age was 35 years (inter-quartile range [IQR] 23-65) and they had worked for a median duration of 56 months (IQR 4-204).

Adherence to PrEP delivery guidelines

At the initial PrEP visit, all (n=25) clinics provided HIV testing, one-on-one PrEP education, HIV risk and clinical eligibility assessment and adherence counselling prior to PrEP initiation (Figure 5). All clinics also asked clients to return one month after PrEP

initiation for refills and review. However, creatinine testing was conducted by only 12 (48%) of the clinics some of the time and not at all by 13 (52%) of the clinics. Only six (24%) clinics reported completing clinic encounter forms fully all the time.

Table 2: Health Providers participating in key informant interviews (n=36)

	N (%) or median (IQR)
Gender, Female	20 (56%)
Age, years	35 (23-65)
Work experience, months	56 (4 - 204)
Cadre Clinical Officers HIV Testing Counsellors Nurses Social Workers Data Clerks Pharmaceutical Technologists	 14 (38%) 8 (22%) 7(19%) 4 (11%) 2 (6%) 1 (3%)

At follow up visits, all clinics conducted adherence counselling. Almost all clinics (n=23, 92%) reported doing an HIV test at month 1 and then at quarterly visits consistently. One clinic reported not doing HIV testing at month 1, and another reported doing HIV testing at all visits including monthly refill visits. Both of these clinics later reverted to testing as prescribed in the guidelines. While the guideline stipulated that clients return to clinics for monthly PrEP refills, the majority of clinics issued more than one bottle of PrEP some (n=15, 60%) or all (n=8, 32%) of the time at follow up visits. Almost none of the clinics (n=2, 8%) always discontinued PrEP when their known HIV+ partner(s) attained viral suppression. The clinic encounter form was fully completed all the time at follow up visits in only 5 (20%) clinics.

Modifications to existing public HIV care clinic practices

All clinics (n= 25) incorporated PrEP-related topics in their regularly scheduled health talks (Figure 6 and Table 3). They also made phone calls to reach their PrEP clients who failed to attend scheduled visits. The majority of clinics included PrEP discussions in their routine facility meetings (n=20, 80%) and also fast-tracked PrEP clients (i.e., escorting them directly to the clinical room and pharmacy, so that they do not queue) (n=20, 80%). Other frequently instituted practices included on-the-job training by colleagues skilled in PrEP delivery (n=15, 60%), including PrEP discussions at already existing ART support groups or at newly constituted PrEP groups (n=13, 52%), providing PrEP services outside of regular clinic hours (n=5, 20%) and dispensing PrEP medication in a clinical room rather than in pharmacy (n=3, 12%).

PrEP uptake and continuation

By December 2018, 4136 people had initiated PrEP at an average of 8 initiations per clinic per month and 55% of individuals were continuing to use PrEP 6 months after initiation across the 25 clinics.

Clinics that did not require creatinine testing at PrEP initiation visits had higher mean monthly PrEP initiations compared to those that required testing some of the time (9.2 vs 6.9 initiations per month) (Figure 7a). Additionally, clinics that included PrEP in their meeting agenda (8.5 vs 6.6), conducted peer PrEP training (9.5 vs 6.1) and fast-tracked PrEP clients (8.3 vs 7.4) had higher mean monthly PrEP initiations compared to clinics in which there was no report of adoption of these practices.

The mean 6-month continuation was higher among clinics that did not require creatinine testing (58% vs 53%), included PrEP discussions in their meeting agenda (58% vs 46%), had refill times greater than a month (58% vs 51%), provided PrEP services outside of regular clinic hours (62% vs 54%) and dispensed PrEP in clinic rooms (66% vs 54%) (Figure 7b).

Provider perspectives on modifications

PrEP providers described reasons for and successes resulting from the changes made to PrEP delivery guidelines and modifications made to routine clinic practices. These reasons are presented in four categories.

To address client needs

Health providers often instituted practices to meet the needs of PrEP clients. They reported that PrEP users did not want to be seen in an HIV clinic due to the stigma associated with the clinics. Long waiting times in the facility were believed to increase the likelihood that they would be spotted by someone known to them, who would label them as HIV-infected. To address this concern, health facilities instituted fast-tracking, in which PrEP users did not queue but were escorted directly to the clinic and pharmacy.

> *[PrEP clients] feel the services are better [now] and they feel they are cared for as compared to the initial stages where we were not fast tracking. [Before] they felt they were stigmatized especially, you know, their neighbors...[who] are*

saying that this person is nowadays taking ARVS. But since we started fast tracking them, … they feel they are being cared for. (KII, Clinical Officer)

Other practices aimed at addressing waiting time and stigma associated with being in a HIV clinic included dispensing PrEP in clinic rooms rather than having them queue in pharmacy and providing services outside of regular clinic hours.

Another modification adopted to address client needs was continuing their PrEP prescriptions, even if their partners had attained viral suppression. Health care providers reported that PrEP users often did not want to give up their PrEP medication as they had no guarantee that their partners would remain virally suppressed.

They [PrEP clients] talk about the fear, they fear that they are being exposed and they can contract HIV. In fact, most of our clients, their partners are virally suppressed and they feel that they should not stop so you cannot force them, you can't force them to stop. (KII, HIV Testing Provider)

To address provider needs

Clinics made adaptations to address challenges that providers faced, especially those related to increased workload. For example, if they were short staffed, some clinicians preferred to make side notes rather than spend time completing the entire client encounter form. In addition, because there were only a few providers who had attended formal PrEP trainings, health workers made efforts to train their peers how to provide

PrEP services. On-the-job training (OJT) was instituted in some facilities upon realization that when those formally trained in PrEP were not available, PrEP eligible persons were sometimes unattended.

> *At first, because only two people had gone for the training so it was difficult… … [T]he clinical officer and the records officer were the [only] ones issuing PrEP but now an OJT was done and all of us as the clinical officers, we were updated about PrEP. So now it is on a rotational basis. Everyone does that [PrEP] delivery per week, so it is easier now than before. (KII, Clinical Officer)*

Improve PrEP uptake

Most health facilities opted to not require creatinine tests before PrEP initiation as many clients could not afford to do them. Although, providers often stated that they would like to have creatinine test results, they knew that if they insisted on having this test, many people would leave without initiating PrEP.

In all HIV clinics, topics related to PrEP were introduced in routinely conducted health talks in order to increase PrEP awareness among people living with HIV and encourage them to bring in their partners to receive PrEP.

> *One of the things that we do to create demand creation in the facility is to give effective health talks in the facility. We are able to educate our clients on PrEP, the eligibility criteria for PrEP, and that makes people to come for PrEP. (KII, Social Worker)*

Improve continuation

Many clinics reported having meetings in the facility during which they discussed strategies to improve PrEP continuation. For example, shortly after starting PrEP services, health providers began to notice that their clients were not returning as scheduled and they began calling them, as they do in HIV treatment programs.

> *Literally we would just leave them [PrEP clients] to come and when we realize a patient has not come, we start doing follow up. So, we have decided to be calling them two days prior to their clinic day. (KII, HIV Testing Provider)*

Many clinics issued more than one bottle at quarterly visits, when they realized PrEP users failed to come for refills because frequent visits posed a burden and interfered with their day-to-day activities. Having longer refill dates was reported as welcomed by PrEP users, as well benefitting health providers by reducing workload.

> *If you give them a shorter TCA, let's say one month, they will not be around to pick their drugs. So, if you give them longer TCAs according to their convenience then it will always improve their retention. (KII, Nurse)*

Discussion:

Health providers made innovative adaptations to activities detailed in PrEP guidelines and instituted modifications to routine practices. These changes were made to simplify

PrEP delivery processes for clients and to reduce service delivery barriers among health workers.

Public HIV care clinics were adherent to most of the requirements laid down in the guidelines, including HIV testing, behavioral risk assessment, PrEP education and adherence counselling. While creatinine testing was required, there was no clinic that conducted creatinine testing all the time at PrEP initiation possibly because guidelines advised that lack of creatinine results should not delay initiation. All facilities made modifications to some of their existing HIV care program practices in order to improve the ease with which clients obtain PrEP from HIV care clinics and to facilitate the integration of PrEP service delivery with available human resources and existing infrastructure. Clinics that instituted contextual modifications such as PrEP discussions in routine facility meetings, on-the-job PrEP training by peers, multi-month scripting and providing PrEP services outside of regular clinic hours had higher than average monthly PrEP initiations and continuation rates.

Adaptations to activities laid out in PrEP guidelines and modifications to routine HIV clinic service delivery practices were aimed at strengthening a client-centered delivery approach. In other studies, long waiting times, frequent visits (that interfere with work schedules and have associated transport costs), stigma, and lack of confidentiality have been identified as barriers to engagement in care [66-68]. Client-centered approaches directed at reducing these barriers and maximizing convenience and responsiveness to client needs and preferences have resulted in continued engagement in care and

improved patient outcomes in HIV treatment programs [69,70]. In our project, health facilities similarly made modifications to their existing practices to reduce time spent seeking PrEP services and address stigma. Additionally, providers accommodated user preferences by not insisting on PrEP discontinuation even when their known HIV infected partners attained viral suppression. Client-centered approaches for HIV prevention programs, including PrEP, have the potential to ensure increased access and efficacious use of HIV prevention strategies [71].

Health facilities instituted practices to lessen the effects of increased workload resulting from integrating PrEP delivery, such as training additional staff members and reducing the frequency of refill visits. Additional strategies to reduce workload burden and address staff shortages common in public health facilities might include task-shifting, use of lay health workers and tele-consultations [72-75]. Cost-effective training approaches such as on-the-job training by peers can increase the number of health workers able to provide PrEP services and in this way address shortages of PrEP-skilled staff [76-78]. Completion of program records should be simplified and standardized and inefficiencies in the data collection system eliminated [79]. Developing electronic medical records for the PrEP program, may improve PrEP data collection systems and enhance data quality in public health facilities [80,81].

Adaptability of an intervention is a key determinant of successful intervention implementation and scale-up [30,82-84]. Therefore, there is need to advance our understanding of adaptations and delivery of evidence based interventions using data

from real-world practice “where the rubber meets the road” in order to facilitate adoption and widespread implementation [62]. Research reporting on the full range of modifications and adaptations made to interventions in routine care settings is limited [62,85]. In this study, we used the expanded framework for reporting adaptations and modifications (FRAME) to comprehensively characterize adaptations to PrEP implementation guidelines and to existing HIV care program practices in order to facilitate PrEP implementation in public HIV care clinics [31]. Using this framework ensured that elements of the adaptations were examined and reported systematically. An important attribute of FRAME is its flexibility that enabled reporting aspects of modifications and adaptations that were relevant and applicable to this intervention. For example, the “adaptation timing” element of the FRAME was not relevant in our study as all modifications were instituted post implementation. Reporting modifications within this framework may be especially useful to others scaling up PrEP programs as it enables an interrogation of the nature, context and goal of adaptations in detail.

A limitation of this study is that providers could have instituted changes in their practices and failed to mention it in the interviews. We endeavored to mitigate this limitation through triangulation of key-informant interviews with different cadres and with technical assistance reports. Another limitation is the observational and descriptive nature of our study which limited our ability to draw conclusions about causal effects of observed adaptations and modifications on PrEP uptake and continuation.

Conclusion:

During the early years of PrEP scale-up in Kenya, HIV care clinics made contextual modifications and adaptations to improve “fit” for PrEP users and providers and improve PrEP uptake and continuation. These findings may inform PrEP delivery in other health facilities in the country and programs in the region.

Competing interests

No conflicts of interest to report.

Authors’ contributions

EMI and GO conducted the analysis and wrote the first draft of the manuscript. JMB, NRM and EAB lead the project, and JO and EW oversaw implementation in study sites. All authors (EMI, JO, EW, EAB, NRM, KN, JFM, KKM, JMB, GO) have read and approved the final manuscript.

Acknowledgements

We thank the leadership and staff of the public health facilities who participated in this study for their motivation and dedication.

The study was funded by the National Institute of Mental Health of the US National Institutes of Health (grant R01MH095507) and the Bill & Melinda Gates Foundation (grant OPP10556051).

Figure 5: Adherence to PrEP delivery guidelines

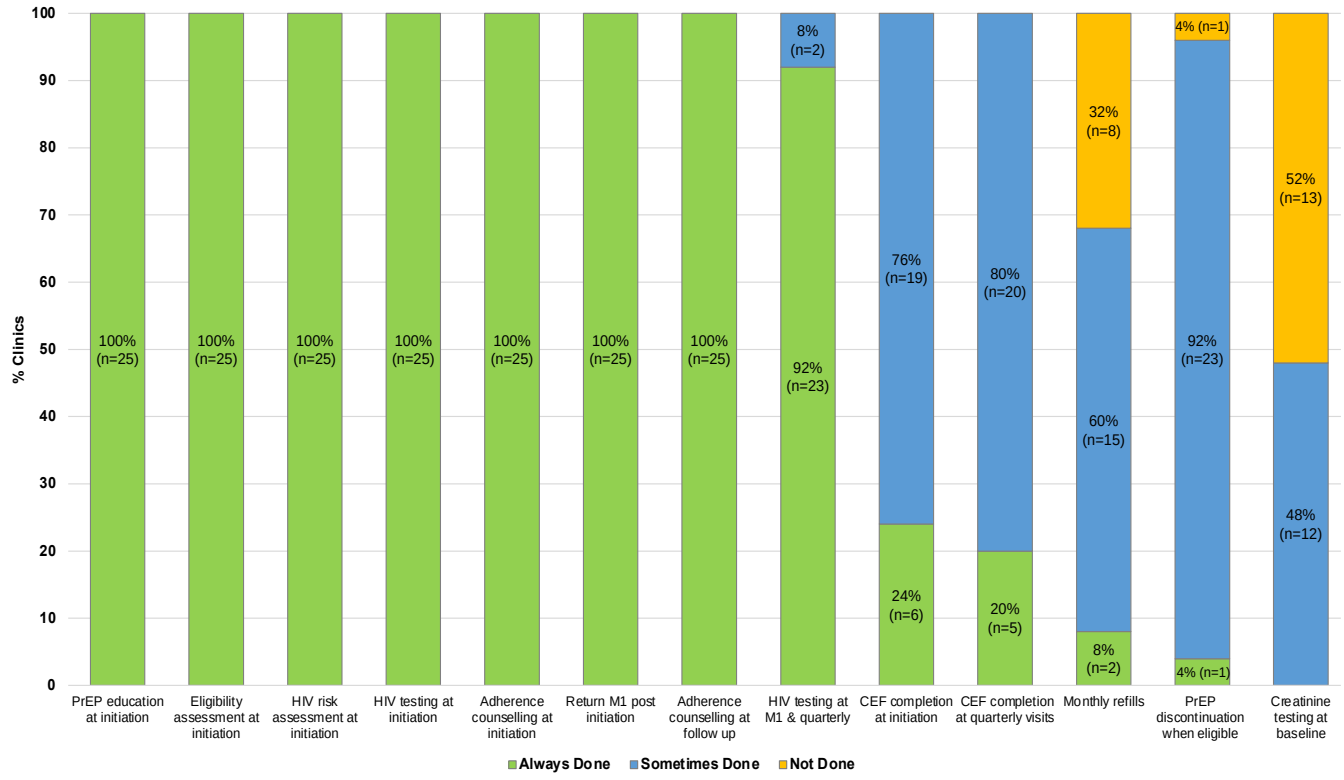


Figure 6: Modifications made by public HIV care clinics to existing HIV care program practices to facilitate PrEP delivery

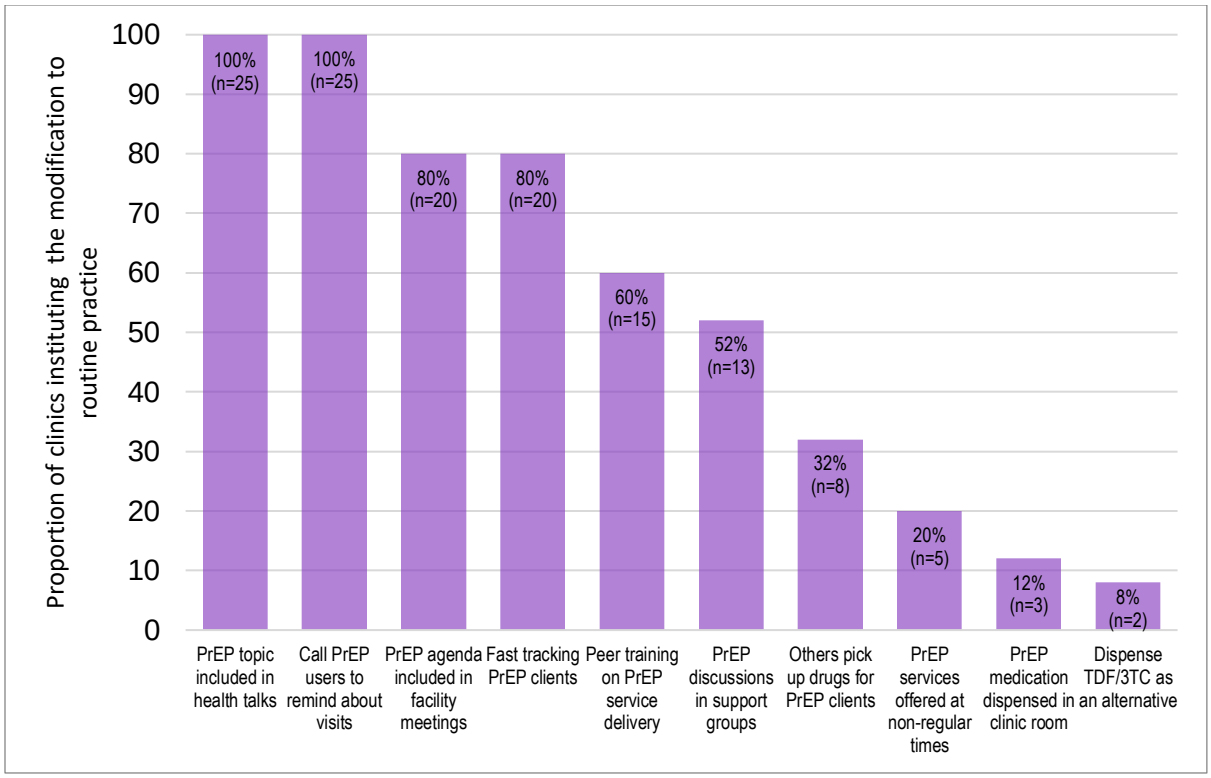


Figure 7: Mean a) PrEP initiations and b) Month 6 continuation among clients at clinics that adopted specified modifications compared to clients at clinics that did not

a) PrEP initiations

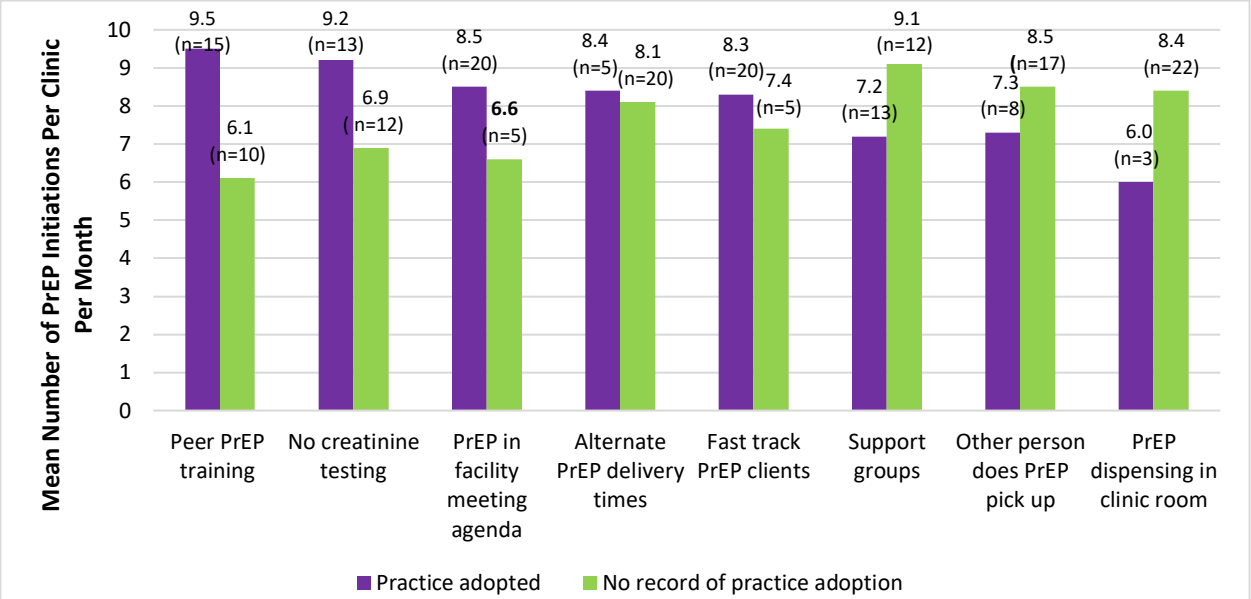


Figure depicts mean number of individuals initiating PrEP at facilities which did (purple) or did not (green) implement specified modifications

b) PrEP continuation at month 6

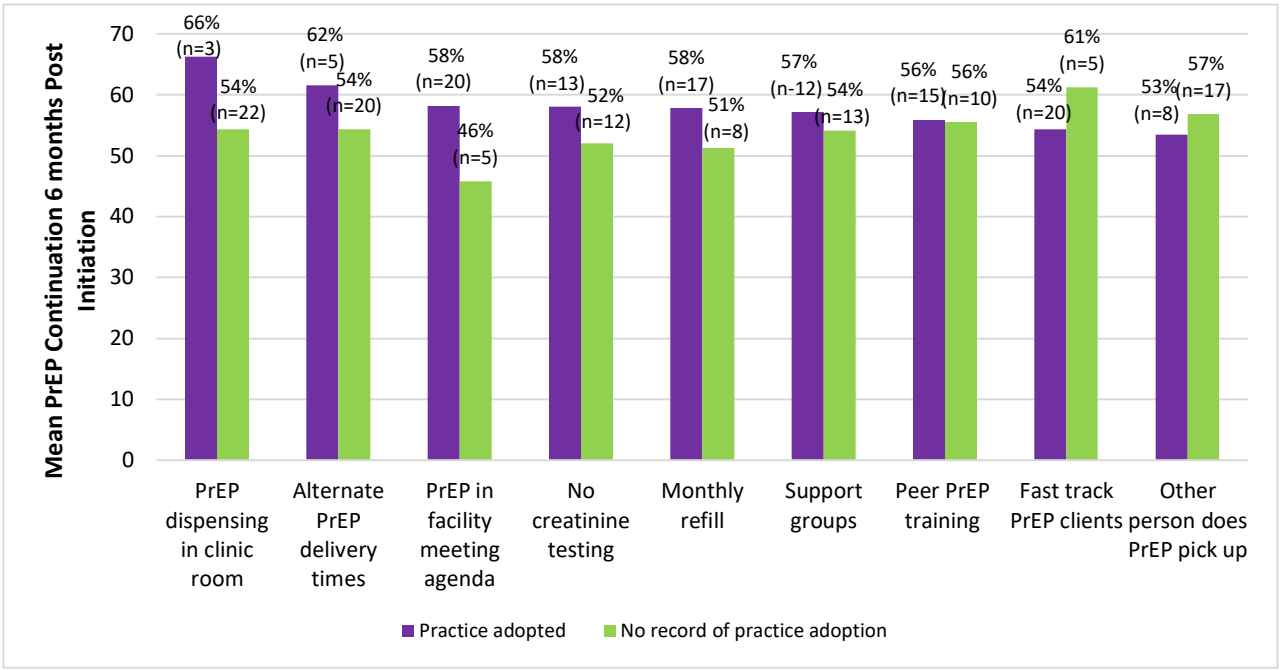


Figure depicts proportion of all individuals initiating PrEP who were continuing to use PrEP at 6 months in facilities which did (purple) or did not (green) implement specified modifications

*Creatinine: purple bar – no creatinine testing done; green bar – creatinine testing done sometimes:
Monthly refill: purple bar - refill intervals longer than a month; green bar – monthly refill intervals

Table 3: Adaptations to content in PrEP implementation guidelines and to the context in which PrEP services are offered

Activity	Description	Description of Adaptation	Nature of Modification	Who participated in decision to modify	For whom the modification was made	Goal of modification
Creatinine testing	Creatinine testing is recommended at PrEP initiation, but absence of results should not delay PrEP initiation	No clinic did creatinine testing for all people initiating PrEP. Most clinics had some testing or no testing at all	Content modification with removal of elements	PrEP program managers at national level Individual health provider	Health facility PrEP User	Increase PrEP uptake as creatinine tests are costly and not readily available
Frequency of PrEP refills	PrEP medication should be issued monthly	At quarterly visits most facilities issued PrEP medication that exceeded one-month supply	Content modification with tailoring of elements	Individual health provider Health facility managers	PrEP User	Increase convenience for PrEP users Improve continuation
Discontinuation of PrEP	PrEP should be discontinued when HIV risk ends	PrEP is discontinued not only when there is no HIV risk but also	Content modification with tailoring of elements	Individual health provider	PrEP User	Increase satisfaction among PrEP users

		when the PrEP user is ready to discontinue				
PrEP-related health talks	Health talks on various topics are conducted at waiting bays routinely	Health facilities incorporated PrEP education in their health talks	Content modification with addition of elements	Health facility managers	Potential PrEP users Partners of potential PrEP users	Increase awareness about PrEP Improve PrEP uptake
Phone calls about scheduled appointments	Health workers routinely make phone calls to remind ART clients about their upcoming or missed appointments	Health workers included PrEP users in their list of individuals to be called	Content modification with addition of elements	Health facility managers Individual health provider	Health facility PrEP users	Improve PrEP continuation at facility level Improve adherence to scheduled visits
PrEP agenda included in facility meetings	Health facilities routinely held meetings to discuss HIV service delivery	PrEP service delivery was included as a discussion item in routine facility meetings	Content modification with addition of elements	Health facility managers	Health facility PrEP users	Improve service delivery Improve uptake Improve continuation
Fast-track PrEP users	People at HIV clinics queue for their services, and	People initiating or continuing PrEP use do not wait in queues but are fast-	Contextual modification to delivery setting	Health facility managers	PrEP users	Reduce waiting time Reduce stigma

	fast-track very sick patients	tracked through service delivery points		Individual health provider		Improve continuation Increase satisfaction
PrEP training by peers	On-the-job-training by skilled peers for HIV treatment services	PrEP service delivery added as a skill to be trained by skilled peers	Content modification with addition of elements	Health facility managers Individual health provider	Individual health provider	Increase number of providers able to provide PrEP services Reduce workload
Support groups	Support groups are held among HIV infected persons and their partners to discuss living positively	PrEP incorporated in discussions held at support groups. In some clinics, support groups specifically for PrEP users were set up.	Content modification with addition of elements	Individual health provider Health facility managers	Potential PrEP users Partners of potential PrEP users PrEP users	Increase awareness about PrEP Improve PrEP uptake Improve PrEP continuation
Allow others to pick up drugs	Clients do PrEP refills in person	Health facilities allowed partners of PrEP users to pick medication for them when they could not come to the clinic	Contextual modification to format of delivery	Individual health provider	PrEP users	Improve PrEP continuation

PrEP delivery outside of regular clinic hours	PrEP services offered during regular hours	Some clinics offered PrEP services at non-regular clinic hours e.g., late afternoon or on days when the clinic is least busy	Contextual modification to delivery setting	Health facility managers	PrEP users	Improve PrEP continuation Reduce waiting time Reduce stigma Increase client satisfaction
PrEP dispensed in clinic rooms	PrEP medication dispensed in pharmacy	A few clinics dispensed PrEP medication in the clinic rooms rather than asking clients to get served in pharmacy	Contextual modification to delivery setting	Health facility managers	PrEP users	Improve PrEP continuation Reduce waiting time Reduce stigma Increase client satisfaction

Description of the modifications is guided by the FRAME: an expanded framework for reporting adaptations and modifications to evidence-based interventions[31]

Chapter 4: Using an on-site modular training approach to amplify PrEP service delivery in public health facilities in Kenya

Citation: Irungu, E., Musau, M., Nyerere, B., Dolla, A., Kwach, B., Owidi, E., Wamoni, E., Odoyo, J., Mugo, N., Bukusi, E., Mugwanya, K. and Baeten, J. M. Using an on-site modular training apporach to amplify PrEP service delivery in public. health facilities in Kenya. Human Resources for Health (*under review*)

USING AN ON-SITE MODULAR TRAINING APPROACH TO AMPLIFY PREP SERVICE DELIVERY IN PUBLIC HEALTH FACILITIES IN KENYA

Elizabeth Irungu[1, 2], Moses Musau[1], Bernard Nyerere[6], Anabelle Dollah[6], Benn Kwatch[6], Emma Owidi[1], Elizabeth Wamoni[1], Josephine Odoyo[6], Nelly Mugo[1, 2], Elizabeth Bukusi[2, 5,6], Kenneth Mugwanya[2], Jared M. Baeten[2,3,4*] for the Partners Scale-Up Project Team

Affiliation

[1]Centre for Clinical Research, Kenya Medical Research Institute, P. O. Box 20778-00202 Nairobi, Kenya

[2]Department of Global Health, [3]Epidemiology, [4]Medicine, [5]Obstetrics and Gynecology, University of Washington, 325 Ninth Avenue, Seattle, WA 98104, USA

[6]Centre for Microbiology Research, Kenya Medical Research Institute, P. O. Box 20778-00202 Nairobi

*Present affiliation: Gilead Sciences, Foster City, USA

Corresponding author:

Elizabeth M. Irungu

P. O. Box 104018-00101

Nairobi, Kenya

Tel: +2546722561

Email: eirungu@pipsthika.org

Funding

The Partners Scale-Up Project is supported by the National Institute of Mental Health of the US National Institutes of Health under grant R01 MH095507 and the Bill & Melinda Gates Foundation under grant OPP1056051.

Key words

PrEP scale up; public HIV care clinics; health care providers; modular training; Kenya

Abstract

Background

Delivery of oral PrEP, a potent HIV prevention intervention, has begun within public health systems in many countries in Africa. Training as many health providers as possible expeditiously is necessary to efficiently and rapidly scale up PrEP delivery among at risk populations and thereby realize the greatest impact of PrEP.

Methods

We designed and implemented an innovative on-site modular training approach delivered in five two-hour modules. The modules could be covered in two consecutive days or be broken across several days enabling flexibility to accommodate health provider work schedules. We assessed knowledge gain comparing pre-and post-training test scores and determined monthly PrEP uptake for six months following the training intervention. We also evaluated the cost of this approach and conducted key informant interviews to explore acceptability among health providers.

Results

Between January 2019 and December 2020, 2111 health providers from 104 health facilities were trained on PrEP. Of 1821 (83%) providers who completed both pre- and post-tests, 505 (28%) were nurses, 333 (18%) were HIV counsellors, 276 (15%) were clinicians and 255 (14%) were lay providers. The mean score prior to and after training was 58% and 82% respectively ($p < 0.001$). On average, health facilities initiated an average of 2.7 (SD 4.7) people on PrEP each month after the training, a number that did not decline over six months post-training ($p=0.62$). Assuming Ministry of Health costs, the costs per provider trained was $16.27. Health providers expressed satisfaction with this training approach because it enabled many providers from a facility receive training.

Conclusion

On-site modular training is an effective, acceptable and low-cost way to provide PrEP education for health workers in public health facilities. This method of training can be scaled up to rapidly amplify the number of health workers able to offer PrEP services.

Introduction

Of the estimated 38 million people living with HIV globally, more than 25 million live in sub-Sahara Africa, making it a region disproportionately burdened with HIV.[1] In 2019, close to 60% of the estimated 1.7 million new HIV infections were from the region and over 400,000 people died from the disease. In September 2015, the World Health Organization (WHO) recommended pre-exposure prophylaxis (PrEP) using oral daily medication tenofovir disoproxil fumarate (TDF), in combination with emtricitabine (FTC/TDF), for HIV prevention among people at risk of acquiring HIV.[14,36] Successful implementation of PrEP in the region is needed in order to attain impactful coverage and meet HIV-prevention goals.

Many countries in Africa have instituted PrEP programs, but scale up has been sub-optimal.[13,56,86] Improving providers PrEP education is essential to foster PrEP implementation and scale up,[87,88] as trained health workers are more willing to discuss PrEP services with their clients.[54,89,90] In addition, health workers who are knowledgeable about PrEP and are competent in PrEP service delivery will identify individuals at risk of HIV acquisition, initiate them on PrEP and conduct follow up visits.[87]

National roll out of the Kenyan PrEP program began in 2017.[17] Over 90,000 people have initiated PrEP in the country making it the second largest program in the continent.[12] However, only a limited number of health care providers in Kenya are trained on PrEP service delivery creating a barrier to expanding PrEP service delivery in

public health facilities.[44,91] Training as many health providers as possible expeditiously is necessary to rapidly scale up PrEP delivery among at risk populations and thereby realize the greatest impact of PrEP in the country.

Here, we describe the implementation of an innovative on-site, modular PrEP training in public health facilities to amplify the number of providers knowledgeable and competent to offer PrEP services in Kenya. We evaluated the effectiveness and cost of this approach and explored acceptability among health providers.

Methods:

The Partners Scale-Up Project is an implementation science project that aims to catalyze national scale up of PrEP in public HIV care clinics in central and western regions in Kenya (Clinicaltrials.gov NCT03052010).[21] The project initially focused on 25 high-volume clinics, then expanded to include training and providing technical assistance to health workers in additional facilities. The present report focuses on trainings developed within the first 25 clinics then implemented in the additional clinics.

Within this project we implemented on-site modular PrEP training sessions in public health facilities in Kenya. We first developed training modules i.e., self-contained sections that when combined with other sections constitute the entire PrEP training curriculum. These were modified from the national PrEP training curriculum that has been described elsewhere.[17,44] In brief, the curriculum had content on determination of PrEP eligibility, tasks to be performed at PrEP initiation and follow-up visits, commodity management and monitoring and evaluation (Table 4). The modules could be covered

in two consecutive days or be broken across several days enabling flexibility to accommodate health provider work schedules.

The county HIV/AIDS leadership, including health facility management in collaboration with technical assistants from the project identified health facilities that would receive training. Health facility management then determined the providers who would be trained, identified the training venue within the health facility where the training sessions would be conducted and proposed training dates that were convenient for them. On-site training within the health facility allowed as many providers as were available to participate. The training sessions were co-facilitated by project staff and PrEP trainers from the county, if available. Each participant received a training manual, a manual of procedures for providing PrEP services, and stationery. Interactive learning methods including the traditional didactic approach, clinical case discussions, and role-plays were applied throughout the in-person training. The duration for each module was two hours. Refreshments were offered during the training, but transport reimbursement was not provided.

Data collection and analysis

Knowledge gain and PrEP uptake

A pre-test assessment was administered to the trainees prior to the start of the training. The same tool was administered at the end of the last module in order to assess training effectiveness in terms of knowledge gain following exposure to training content. This assessment was the same as the one developed for the standard national training

curriculum. Providers were considered to have completed the training if they completed both pre-and post-test assessments. We computed the mean scores for the pre- and post-tests and using a paired t-test, compared mean pre-and post-test scores among providers who completed the training.

Using programmatic data obtained from health facilities at the beginning of training and for 6 months thereafter we obtained the number of individuals initiating PrEP per facility and ascertained the mean monthly PrEP uptake across health facilities following the modular training. To determine whether the number of monthly PrEP initiations per clinic changed over the six-month period after modular training, we conducted an analysis using a negative binomial mixed effects model with log link. The model included month since training and training year as fixed effects and a random effect for each health facility. Analyses were conducted using R software 3.5.2 and Stata version 15 (StataCorp, College Station, TX).

Cost Analysis

In fourteen randomly selected health facility trainings, we conducted activity based micro-costing following established guidelines to determine the programmatic cost per provider trained assuming implementation by the Kenyan Ministry of Health.[92] We obtained costs of training implementation from project expense reports and receipts. We included costs of training materials (including training manuals and stationery), refreshments, and training facilitator time. We obtained health provider salaries from published Kenyan civil service salary scales.[93] We excluded project related costs that would not be applicable in programmatic roll out such as travel and accommodation costs for project staff trainers and replaced project staff salaries with public sector

salaries. We did not include costs of developing the training curriculum since the existing curriculum could be scaled to additional facilities as-is.

We computed the average cost of a modular training as the sum of training costs of the randomly selected trainings divided by the number of trainings. The cost per provider trained was then calculated as the average cost of modular training divided by the average number of providers per training. Expenditures reported in Kenyan shillings were converted to United States dollars (USD).[94] Analyses were conducted in Excel (version 16.5, Microsoft, Redmond, WA).

Qualitative interviews

Using a semi-structured guide, we conducted in-depth interviews with 35 health providers who attended modular training sessions to gain a deeper understanding of the training experience and acceptability of the modular training approach. We purposively sampled health providers of varied cadres in different health facilities to capture different perspectives. Interviews were conducted in English face-to-face or via telephone and recorded. They were then transcribed verbatim. Transcripts were analyzed in Dedoose (Sociocultural Research Consultants LLC, Los Angeles, CA). An initial codebook was developed deductively from the interview guide. Additional codes were added inductively as initial transcripts were reviewed and coded. The first three transcripts were double coded by at least two members of the study team and inconsistent results were reviewed by the coders until consensus was reached. The remaining transcripts were coded independently by one member of the study team and reviewed by another

member. After all data were coded, investigators used an iterative process of reading transcripts, comparing and contrasting coding, and identifying convergent and divergent themes within and between transcripts.

Ethical review

Ethical approval for this project was obtained from the University of Washington Human Subjects Division and the Kenya Medical Research Institute Scientific Ethical Review Unit. Written informed consent was provided by all health workers participating in-depth interviews; quantitative program data was deemed part of quality assessment and thus not requiring individual consent.

Results

Knowledge gain and PrEP uptake

Between January 2019 and December 2020, 2111 health providers from 104 health facilities received on site PrEP training using the modular training approach. The median number of participants per training was 19 (inter-quartile range 14-25). Of 1821 (83%) providers who completed both pre- and post-test assessments, 505 (28%) were nurses, 333 (18%) were HIV counsellors, 276 (15%) were clinicians and 255 (14%) were lay providers. The mean score prior to and after training was 58% and 82% respectively ($p<0.001$). Mean scores for all cadres increased significantly ($p<0.001$) after training compared to before training (Fig 8).

Over a six month follow up period post training, health facilities initiated an average of 2.7 (SD 4.7) people on PrEP per month, and this rate of PrEP initiations was consistent over the six months (p=0.62).

Cost of modular training

The overall project cost of implementation of on-site PrEP modular training across the 14 randomly selected facilities was $387 per facility training. The expected programmatic costs of implementing on-site modular training, assuming Ministry of Health costs is $315 per training and $16.27 per provider trained. Training materials, refreshments and trainer facilitation fees contributed 38%, 32% and 30% of the costs, respectively (Fig 9).

Acceptability of modular training

Health providers reported that they gained knowledge from the training and felt competent enough to inform their clients about PrEP and offer PrEP services. They liked this training approach because it enabled many staff members, including key front-line providers and those working in various departments receive PrEP training. On-site training was unlike hotel-based trainings where only a few staff members are selected to participate. Providers reported that the advantage of having many staff members in the facility trained was that they would be comfortable talking to potential PrEP clients wherever they were stationed. They also stated that training together as peers facilitated interactive training sessions with open discussions that addressed facility-specific issues of PrEP delivery. In addition, health providers reported that training within the facility avoided the inconvenience of travelling out of facility for training.

You know at times, you might find someone going for a training but they don't offer the service, they are not the key providers for the service. So, the facility-based training is like an advantage whereby whoever is implementing gets the chance to [get] first-hand information…. Then, an added advantage is even the rest get to know [about PrEP delivery]. (KII, Clinical Officer))

There was a lot of discussion … towards how we can make the delivery better and make our facility also shine in terms of making sure that we have more and more people who are affected by the situation [HIV risk] come and get into PrEP. (KII, Nurse)

However, providers reported disruptions during the training in order to attend to patients, when workload increased. They also stated that they would have wished to receive some money, akin to transport reimbursement provided in out-of-facility trainings.

Discussion

In this evaluation of an innovative on-site modular PrEP training curriculum, we trained over 2,000 health workers over a two-year period and found that health providers of all cadres gained PrEP knowledge following delivery of the curriculum. In addition, participating health facilities initiated at risk persons on PrEP at a rate that did not decline over the first six months after the training.

As PrEP services are largely offered in public health facilities, training all cadres of health providers on PrEP service delivery is paramount.[40,86] Trained front-line providers help their clients think about their HIV risk, they determine their eligibility for PrEP and issue prescriptions to those eligible. As described in other settings, lay providers, when trained, are able to deliver health talks and have one-on-one conversations to educate people about PrEP.[95,96] Providers not primarily involved in PrEP delivery were also included in the training. This was important so that they could identify at-risk individuals from any department in the health facility and refer them to where they could get services. Importantly, training all people working in a health facility is valuable as the community looks to anyone working in health facilities, regardless of their cadre, to clarify PrEP-related information and help dispel myths related to PrEP.[89]

Capacity-building efforts for health workers may be expensive and low-cost PrEP training modalities are urgently needed.[52,97-100] By offering training within health facilities, we did not incur costs of conferencing facilities and transport reimbursement. The on-site modular training approach was thus relatively inexpensive at $16 per provider trained. Other innovative cost-effective training approaches have been utilized including use of web-based training modules and on-job training.[78,101]

The qualitative assessment found that the training impacted health providers' ability to offer PrEP services positively. The on-site modular training approach was acceptable, allowed flexibility with work schedules and in this way enabled many health providers to participate. In addition, the ability to be trained together as members of the same facility

provided an opportunity for the participants to discuss PrEP delivery challenges unique to their facility and explore how to overcome them. Similar to our study, other studies have documented the feasibility and positive impact of on-site HIV-related training approaches.[102,103]

There are limitations to these analyses. We did not have information on monthly PrEP initiation per facility prior to the training, and thus could not assess whether the PrEP initiation trend we observed post training was different from what had been happening in facilities prior to the training. The participating facilities were from central and western regions of Kenya, nevertheless they reflect the spectrum of public health facilities in Kenya, making the lessons learned generalizable to the rest of the country.

Optimizing access to PrEP requires expanding the number of healthcare providers who are knowledgeable and competent to deliver PrEP integrated in routine practice rapidly. On site modular training is an effective, acceptable and low-cost way to provide PrEP education for health workers in public health facilities. This method of training can be scaled up to rapidly amplify the number of health workers able to offer PrEP services.

Acknowledgements

We are grateful to the management and health providers in all participating HIV care clinics.

The Partners Scale-Up Project trainers:

Western team: Josephine Odoyo, Bernard Nyerere, Kenneth Odhiambo, Meresa Oyier, John Bosco Tsetso

Central team: Elizabeth Wamoni, Margaret Mwangi, Roy Njiru, Irene Wanyoike, Winnie Watuika

Competing interests

The authors declare they have no competing interests

Table 4: Modular structure of the PrEP curriculum

	Title	Description of Content
Module 1	Introduction to PrEP	- Provides a background of HIV burden in Kenya - Describes what PrEP is and details PrEP efficacy - Delineates who is eligible for PrEP - Differentiates PrEP from PEP
Module 2	The Service Provider Toolkit	- Guides providers how to conduct risk assessment - Provides guidance for how to initiate PrEP and follow up PrEP users
Module 3	Clinical Case Management	- Allows providers to role play and discuss various case scenarios
Module 4	PrEP Commodity Management	- Details flow of PrEP commodities and ordering processes. - Guides providers how to do pharmacovigilance for PrEP
Module 5	Monitoring and Evaluation for PrEP	- Introduces providers to various reporting tools for PrEP

Figure 8: Pre- and post-test mean scores, by cadre

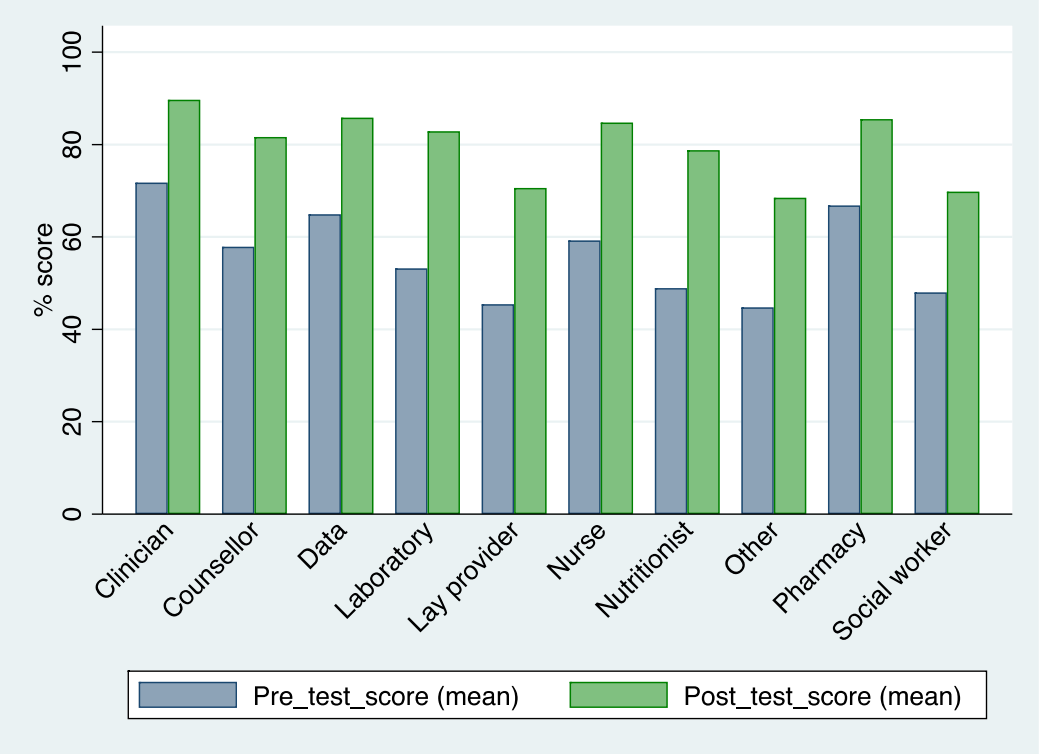
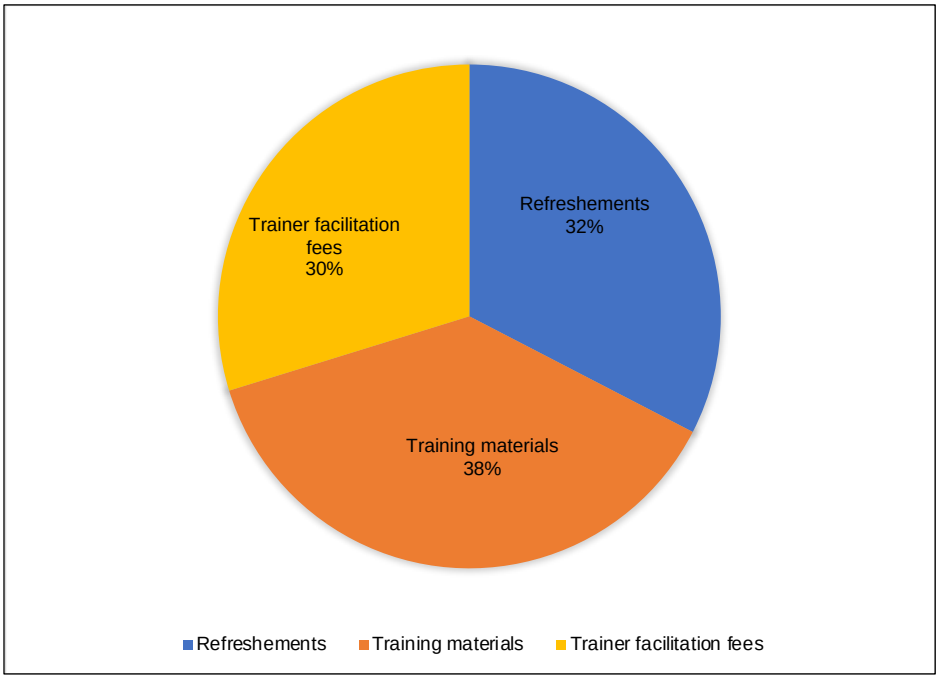


Figure 9: Proportion of costs related to each resource type of on-site modular PrEP training for health providers



Chapter 5: PrEP roll out in Africa: status and opportunity

Published Citation: Irungu EM, Baeten JM. PrEP rollout in Africa: status and opportunity. Nat Med. 2020;26(5):655-64. Epub 2020/05/15. doi: 10.1038/s41591-020-0872-x. PubMed PMID: 32405065.

PrEP roll out in Africa: status and opportunity

Elizabeth M. Irungu[1,2] & Jared M. Baeten[2,3,4]

Affiliations

[1]College of Health Sciences, Jomo Kenyatta University of Agriculture and Technology, P. O. Box 62000-00200 Nairobi, Kenya, [2]Department of Global Health, [3]Epidemiology, [4]Medicine, University of Washington, 325 Ninth Avenue, Seattle, WA 98104, USA

Corresponding author: Jared Baeten
325 Ninth Ave, Box 359927
Seattle, WA 98104 USA
jbaeten@uw.edu

Word count:

Abstract: 148 words
Main paper: 4887 words

Abstract

Following recommendations by World Health Organization in 2015, countries in sub-Sahara Africa, the region with the highest HIV burden, developed policies that incorporate pre-exposure prophylaxis (PrEP) into national HIV prevention strategies. By the end of 2019, more than one-third of people receiving PrEP globally were in Africa. Crucial learning from early roll-out among at-risk populations including HIV serodiscordant couples, adolescent girls and young women (AGYW), female sex workers (FSW) and men who have sex with men (MSM) include the importance of strategies to maintain persistent adherence to PrEP while at risk of HIV and novel approaches to make PrEP services accessible, simplified, and efficient. Additionally, increasing community awareness is absolutely essential to reduce stigma associated with use and accelerate uptake and support continued use. PrEP has the potential to contribute substantially to reversing the African HIV epidemic – maximizing successful delivery at scale is essential to realize this potential.

Introduction

Despite a gradual and modest decline of new HIV cases over the past decade, in 2018, 1.7 million new HIV infections occurred globally, of which 60% occurred in sub-Saharan Africa.[104] Women in Africa are especially disproportionately affected and young women (under 24 years of age) had more than twice the number of new infections compared to young men in 2018.[105] Although the epidemic in this region is generalized (i.e., it affects the population as a whole), key populations and their sexual partners accounted for a quarter of new HIV infections in east and southern Africa and close to two-thirds of new infections in west and central Africa.[104]

Over the past two decades, antiretroviral treatment programs revolutionized HIV care in Sub-Saharan Africa, grounded in substantial global donor investment, national government leadership and policy-making, and community-embedded care that brought life-saving medicines to populations across the continent. HIV prevention has long been part of national policies in African countries, initially with a focus on education and behavior change, then testing and knowledge of status (and partner status), then tremendously successful efforts to scale up prevention of mother to child transmission services, later incorporating scale-up of voluntary medical male circumcision, and most recently boldly expanding eligibility for antiretroviral treatment to all persons living with HIV, capitalizing on the simultaneous health and prevention benefits of viral suppression with effective antiretroviral therapy.

Pre-exposure prophylaxis (PrEP), using the oral daily medication tenofovir disoproxil fumarate (TDF), in combination with emtricitabine (FTC/TDF), was demonstrated to be efficacious and safe for preventing HIV acquisition for both men and women in pivotal studies reported in late 2010 and 2011.[36] Importantly, the registrational evidence for PrEP for HIV prevention comes from two large clinical trials – one among men who have sex with men (MSM) and one among heterosexual men and women with partners living with HIV[3,7] – and both of those trials included African populations, with the heterosexual trial completely based in Africa. This perspective focuses on the current state of PrEP roll-out in African settings, challenges encountered to date, and opportunities that lie ahead.

Challenges to introducing PrEP

In settings worldwide, PrEP has faced challenges to delivery at scale, many expected for a brand-new intervention. Universally, PrEP challenges have included determining and identifying subgroups and individuals who might benefit most from PrEP, establishing systems to link generally otherwise healthy people to ongoing PrEP services, maintaining adherence to the medication, and combatting stigma and discrimination related to being at risk for HIV, a member of a more highly-burdened key population, or even simply being sexually active. For Africa, PrEP is not a stand-alone intervention – its arrival into national programs followed years of work to build out work in HIV testing, prevention services, and treatment and care. Moreover, PrEP delivery has to date largely been integrated into existing programs in public health care systems, which are mostly clinic-based. Those facilities, overburdened and resource-constrained already, found that providing an additional service, particularly an unfamiliar one

targeting generally younger and healthy people, presented unique challenges. A notable challenge for PrEP delivery has been that facility-based care may not always be accessible or acceptable to all. For example, HIV care clinics may be acceptable to HIV serodiscordant couples, since one member may be attending that facility for care already, but many members of key populations and young women would prefer facilities that appeal more specifically to them. PrEP services in Africa are often provided free-of-charge, however transportation costs and wages lost on clinic days may be a hindrance to uptake and continued use.[106] Moreover, in resource-limited settings in Africa, PrEP service delivery adds a new cost to tight budgets, both for countries and for global donors who are key players in HIV prevention and treatment. Thus, lack of access to PrEP is simply because it has not been incorporated into national prevention programming or, even if it has, it has not been expanded to all localities. Another challenge to delivery is low community awareness and knowledge of PrEP, yet this is critical in fostering PrEP demand generation, maximizing its acceptability and supporting use.

Current status of PrEP roll out in Africa

In January 2011, the United States became the first country to issue guidance recommendations for the use of PrEP; formal regulatory approval followed in the US (specifically for FTC/TDF) in July 2012.[107,108] In September 2015 the World Health Organization issued guidance recommending oral PrEP, using TDF-based medications (FTC/TDF, or lamivudine [3TC]/TDF, or TDF alone), for persons at substantial risk of HIV infection (defined as an anticipated incidence higher than 3 per 100 person years),

in combination with other prevention strategies.[14,109] To date, drug regulatory authorities in 12 African countries have approved a formal indication for PrEP and national policies in 9 countries in Africa have incorporated PrEP as part of prevention strategy.[110] TDF, alone or in combination with FTC or 3TC, was included on the WHO Essential Medicines List in June 2017. As of October 2019, an estimated 136,150 - 144,050 persons have initiated PrEP in Africa (Figure 10a), with Kenya, South Africa, Zimbabwe, and Uganda currently having the largest PrEP programs in Africa. The size of PrEP programs to date generally reflects epidemic size (Figure 10b) across African countries, with countries that have high HIV prevalence having the largest PrEP programs, although the availability of external donor funds and political will have also driven the pace of scale-up in individual countries and explains differences between number of initiations and size of ongoing epidemic.

Clinical trials and implementation of PrEP

Randomized, placebo-controlled trials of PrEP definitively demonstrate its safety and efficacy for HIV prevention (Table 5). However, Indeed, a striking finding of PrEP trials was that not all individuals were adherent, and subsequent work helped to characterize that some individuals struggled with adherence to daily medication for HIV prevention and others did not adhere to a medication that had not yet been proven safe and effective. For individuals who were adherent, post hoc analyses from the clinical trials found that HIV protection was very high, with global consensus estimating >95% protection for both men and women. To bridge from clinical trial data to delivery at scale, demonstration projects are recommended by the WHO and initiated in a variety

of settings.[111] These projects provide real-world evidence for effectiveness and willingness to use PrEP by people at increased HIV risk. Most African PrEP programs have focused on specific subpopulations, targeting PrEP resources to groups with greatest HIV risk; key lessons learned from clinical trials, demonstration studies, and implementation in those groups are summarized here (Table 5).

Serodiscordant couples

Potentially half of new HIV infections in Africa occur within married or cohabiting couples which are HIV serodiscordant (i.e., in which one member is living with HIV and the other HIV negative). [112,113] The Partners PrEP Study was one of two pivotal trials that demonstrated safety and efficacy of PrEP for HIV prevention; it was conducted among 4747 heterosexual HIV serodiscordant couples in Kenya and Uganda.[3] Couple recruitment strategies for this study included partnering with HIV testing centers, community mobilization activities during which there was public promotion of couples HIV testing and distribution of materials that encouraged couple HIV testing. Couples' poor understanding and belief of HIV discordance and health care workers' lack of adequate knowledge how to manage HIV discordant couples are potential barriers to couples-based HIV prevention and care; importantly, couples-based HIV testing is a recommended by WHO and an important part of HIV control strategies across Africa.

To enhance understanding of the feasibility and acceptability of PrEP delivery within this population and to inform scale up of PrEP, two demonstration studies of PrEP in this population were conducted, one in Kenya and Uganda and the second in Nigeria.[8,114,115]

PrEP was delivered as a “bridge to viral suppression by ART” – i.e. the HIV negative partners received PrEP until their partners living with HIV achieved viral suppression, at which time counseling about discontinuing PrEP was recommended. These projects found that couples at high risk of acquiring HIV were interested in taking PrEP and adhered to medication while they were at risk, resulting in a near-elimination of HIV transmission within the partnership.[116-118] Use of PrEP until viral suppression in a partnership is now a delivery approach that has been recommended by WHO among HIV serodiscordant couples worldwide. HIV serodiscordant couples are motivated to use PrEP because it relieves fear of HIV infection within the partnership, enables couples regain intimacy, maintains their relationship, and permits hopes of conception, as described by couples participating in the Partners Demonstration Project and other studies.[119-122] Within national PrEP programs, including in Kenya, Uganda, and Zimbabwe, close to half of those initiating PrEP are in known HIV serodiscordant partnerships, suggesting great interest.[17,123,124] The ongoing Partners Scale-Up Project is catalyzing uptake of PrEP for HIV serodiscordant couples in 25 public health HIV care clinics across Kenya, demonstrating deliverability in real-world settings.[21,125] Within this project, PrEP delivery services are delivered by Ministry of Health staff - thus moving beyond research study staff and directly to delivery at scale.

Adolescent girls and young women (AGYW)

Globally 6000 young women aged 15-24 years are newly infected with HIV every week, with the majority of those infections occurring in sub-Saharan Africa.[104] Despite frequent and regular risk reduction counselling and access to HIV prevention options, as

provided through school-based programs, youth-friendly clinics and family planning services, HIV incidence among adolescent girls and young women remains high.[126-128] The importance of adherence for PrEP was driven home by the results of the VOICE and FEM-PrEP trials, which failed to show HIV protection from PrEP, as a result of abysmal adherence (<30%) in the trial populations.[6,129] These placebo-controlled trials, done at the same time as the key registrational trials of PrEP,[3,7] recruited women from general population settings in Kenya, South Africa, Uganda, and Zimbabwe.[130] Work done after these studies sought to explain the surprisingly low adherence in the trial populations, with key explanations focusing on challenges with taking a daily pill (particularly as a healthy person), peer, partner and family influences that stigmatized being at risk for HIV (or being thought to have HIV, as only persons with HIV took medication), and substantial concerns in the study population about taking a medication that was unproven and without demonstrated evidence of safety.

Strikingly, though, good uptake and adherence to PrEP has been observed among some women participating in various PrEP open-label and demonstration projects in Botswana, South Africa and Zimbabwe, in part likely because women know that the product they are taking is safe and effective.[131-133] A feasibility study conducted among older women who were female partners of migrant miners in Mozambique also demonstrated high adherence to PrEP.[134] Young women report interest in taking PrEP because it is an empowering HIV prevention intervention they can use in private, that would protect them from HIV in spite of the behaviors of their partners.[121,135,136] For pregnant women, protecting infants from contracting HIV highly motivates PrEP use.[135]

High medication adherence was observed during periconception periods in the Partners PrEP Study.[137] In demonstration projects and open label implementation pregnant women and those desiring fertility used PrEP successfully.[138,139] One important feature of PrEP research has been the rapidity with which expansion to pregnant and lactating populations has occurred; for many medications, safety and use in pregnancy often lags many years behind use in non-pregnant populations.[140]

Uptake of PrEP by AGYW within national PrEP programs has been cautious but promising. In the first year of the Zambian program PrEP was offered in 162 sites across 9 provinces to 3,600 clients with more than a third of those initiating being adolescent girls and young women.[141] Similarly, within a PrEP implementation project for young women and adolescents, in which services were offered in maternal and child health and family planning clinics in western Kenya, one in five screened women elected to initiate PrEP, and close to a half returned for at least one refill visit. [138,142] An ongoing challenge in studies of PrEP among AGYW is one of continuation of PrEP once the program is scaled up. In most studies, a substantial fraction of AGYW starting PrEP do not return for a refill one month after initiating and often the majority discontinue within the first six months, although often a fraction restart PrEP.[143] Defining what is success in PrEP initiation and continuation is a topic of programmatic evaluation, but the ultimate goal is the achievement of substantive reductions in new HIV infections.[144]

Female sex workers

Globally, HIV prevalence among female sex workers is more than twelve times that of the general population as a whole and is extremely high in some parts of Africa, with more than half of sex workers living with HIV.[145-148] PrEP is an HIV prevention intervention that may appeal to female sex workers because they have control over its use, and it enables them to work with less fear, often without condoms, as insisted on by clients and carrying greater compensation.[121,149] A cluster-randomized trial in Zimbabwe, SAPPH-Ire, assessed effect of a comprehensive program that included oral PrEP targeting, on-site ART initiation and community mobilization for female sex workers.[150] The investigators conducted respondent-driven sampling surveys and found that of the sex workers screened and offered PrEP, 38% initiated and of these 81% returned for at least one visit. In Benin, the PrEP demonstration project among female sex workers followed women for a year and demonstrated high uptake and close to half of the cohort remained in follow up at the end of the project.[151] A PrEP demonstration project conducted in Kenya found that 60% of female sex workers initiating PrEP returned for at least one refill visit.[152] South Africa's national PrEP program has grown in a measured stepwise fashion, beginning with delivery for sex workers in 2016. In the first two years, over 4,000 clients had initiated PrEP at 34 sex worker sites. PrEP services were provided at fixed facilities, through mobile vans and through outreach activities to reach sex workers where they are.[153] As part of the Kenyan PrEP program, the *Jilinde* Project has been scaling up PrEP, and among other population prioritizes delivery to female sex workers in drop-in centers. Close to 60% of 9,500 people initiating PrEP within the first eighteen months within this project were female sex workers.[143] The Zimbabwean program begun in 2018 and offers PrEP in centers

dedicated to key populations, public health facilities and community based centers. In the first 18 months of the program over 12,000 people had initiated PrEP with about 50% being female sex workers.[124]

Men who have sex with men

Widespread homophobia in Africa and criminalization of sex between men has been associated with poor health seeking behavior and poor health outcomes among men who have sex with men.[154-156] The risk of HIV acquisition among MSM globally is almost 30 times higher that of heterosexual men.[157] HIV prevention efforts for this population are prioritized. The iPrEx Study was the first completed, randomized, placebo-controlled trial to demonstrate the efficacy of PrEP for HIV prevention; it enrolled 2499 men or transgender women who have sex with men in 6 countries (Brazil, Ecuador, Peru, South Africa, Thailand, United States).[7] Acceptability and willingness to use PrEP among MSM is high and strong motivations for PrEP use include decreased anxiety over risk of HIV, an increased sense of control and a sense of greater intimacy with condomless sex.[158-161] In a Kenyan demonstration project, uptake of PrEP was generally good among the MSM population.[152] To date, within national programs, uptake of PrEP among MSM has varied. The South African PrEP program was phased and deliberately implemented PrEP specifically among key populations including MSM in the early phase of the program. Within the first year of PrEP implementation, over 50% of 2,857 MSM offered PrEP in clinics dedicated to serving MSM took it up.[153] In Kenya, the national PrEP program is directed to all at risk, rather than specifying population types;

nevertheless, in settings catering to MSM, uptake has been high.[143] In Zambia, within the first year of their program, 3% of those initiating PrEP were MSM.[141]

General populations

While emphasis for PrEP delivery has been placed on key populations and other at-risk populations, countries are providing PrEP for the general population, i.e., those not specifically in a key population group (like MSM, AGYW), including men and women who may be at risk of acquiring HIV as a way of normalizing PrEP delivery. A demonstration project in eSwatini which is providing PrEP to general population through public-sector primary care health facilities reported that this approach is enabling and life-improving.[162,163] The Sustainable East Africa Research in Community Health (SEARCH) study which conducted community-level PrEP education and offered PrEP to high risk persons in Kenya and Uganda initiated 3,489 people on PrEP.[164] In the Kenyan program, 15% of people initiating PrEP are general population.[165]

Lessons learned from early implementation of PrEP

There is high interest in PrEP services

People at risk of acquiring HIV are interested in taking PrEP within national programs when they are informed about its effectiveness. Such messaging should be engaging, informative and appealing to the target population.[166] By October 2019, of the estimated 380,000 people who have taken PrEP at least once globally, more than a third were from Africa (Figure 11).[110] It is likely still early to observe population level reduction in HIV incidence associated with PrEP use but the high uptake in Africa is encouraging

especially because the region has the greatest burden of HIV, and is a departure from the past practice where care and treatment for persons living with HIV in the region lagged behind implementation in high-income settings by many years. Across settings the major barrier to PrEP initiation is lack of access.

Best Practices for Communicating about PrEP
Messages should:

1. *Be informative and engaging*
2. *Avoid perceptions that PrEP is for a particular population*
3. *Resonate with the clients' aspirations rather than emphasizing risk*
4. *Inform of PrEP efficacy, expected but infrequent side effects and availability of provider to address any concerns*
5. *Inform of the importance of adherence to medication*
6. *Inform that PrEP is not for life*

Continuation is challenging

Across all populations, while there is great willingness to initiate PrEP, effective continuation has often been lower than expected. Reasons for discontinuation are varied – individuals decide that their risk is not sufficiently high to take PrEP, they determine that a daily pill is not for them or that other prevention strategies are preferred, or they find it difficult to return for refill appointments. Among young women low risk perception, experience of side effects and lack of social support are reasons for discontinuation.[142,152] In the PrEP Implementation for Young Women and Adolescents (PrIYA) project young women initiating PrEP in reproductive health clinics in Kenya were more likely to continue if they had a partner living with HIV and were older (greater than 24 years).[138,142] Among key populations, continuation is driven by continued prevention from HIV and hope for the future.[161] However, stigma is a significant barrier to effective continued PrEP use. A qualitative study among MSM reported that being seen with PrEP would make people think they have HIV, making them vulnerable to

discrimination and rumors in the community and being labelled as promiscuous.[159] These findings were similar to those reported by AGYW, FSW and MSM using PrEP in Kenya.[167] In demonstration and implementation projects continuation among HIV serodiscordant couples is often higher than that of other populations.[124] The Partners Scale-Up Project reported that of those initiating PrEP, two-thirds had returned within three months of initiation.[125] In addition, 96% of randomly selected individuals returning for refill visits had tenofovir detected in their blood. It has been reported that the shared goal within the partnership to prevent HIV transmission and preserve the relationship, results in mutual support to use antiretroviral medication by both partners.[168]

PrEP use should be encouraged when people are at risk for HIV and discontinued when risk abates.[48] For this reason, it has been challenging to set continuation benchmarks for PrEP success – essentially, the denominator is constantly shifting.[144] It remains to be understood whether those opting to discontinue PrEP have come out of a “season of risk” and are thus discontinuing appropriately. If they are still at-risk, efforts made to bring them back into programs or to encourage them to use alternative effective prevention interventions. There is anticipation for new PrEP delivery tools including implants and injectable PrEP which will likely address concerns related to daily pill taking.[169] To these ends, studies to understand PrEP continuation rates and reasons why people discontinue use in comparison to other prevention strategies – like contraception for pregnancy prevention – is a priority. Understanding barriers to effective continued use of the daily oral PrEP pill will guide support for the introduction of long-acting PrEP options.

Invest in capacity building health providers

Adequate provider knowledge is a necessary requirement to scale up PrEP services with fidelity.[87,170,171] Additionally, in communities, health providers of all types are often sought for consultation both formally and informally on health issues; thus, it is key that health workers, even those not likely to provide PrEP services, be PrEP-aware. Sensitivity training is essential to address potential negative, moralistic attitudes towards high risk people seeking health services which may impede uptake of PrEP.[172-175]

Several approaches have been employed to increase knowledge and capacity of health providers. National policies and implementation guidelines in most African countries, including Kenya, Zimbabwe and Malawi have proposed using the ”train the trainer’s” model, which generates a cadre of knowledgeable health providers who go on to train others.[16] Hotel-based trainings have been used frequently to train health providers on HIV care and management and now, PrEP.[44] The advantage of this training approach is the uninterrupted, dedicated time availed away from work for training. However, this approach is costly, limiting the number of providers who can be trained. A one-time training of providers may not always be sufficient and regular mentorship and technical assistance is required to encourage providers and help them trouble-shoot early implementation challenges.[21,176]

Simplifying PrEP delivery

PrEP delivery services should be aligned to needs of populations they serve. HIV care clinics are one logical place for PrEP service integration as they have a ready eligible

population (partners of clients living with HIV), health workers stationed there are conversant with prescribing antiretroviral medications, and there is an established commodity supply system.[21,163] However, these clinics are often overcrowded and there is stigma associated with being potentially seen as living with HIV which may prevent attendance at these clinics. Similar to ART, structural barriers such as transportation costs and distance to service delivery points are barriers to PrEP continuation as was reported in the SEARCH study, which did community wide testing and offered PrEP to people in HIV discordant partnerships, those identified as having an elevated HIV risk on the basis of an empirical risk score, or who self-identified as being at high risk in Uganda and Kenya.[51,106]

Key populations such as MSM and FSW receive services at dedicated drop-in-centers. Integrating PrEP into such services that are already available for key populations will enhance accessibility and likely foster sustainability of the program. PrEP programs have also been integrated in reproductive health clinics which provide ante-natal, post-natal and family planning services.[138,142] These clinics offer a ready PrEP-eligible population of sexually active women in their reproductive age and have less associated stigma. Health workers stationed here require training on how to provide PrEP services and how to have discussions about sexual risk especially with young women in an open non-judgmental manner. Youth friendly clinics provide a comfortable environment for young women to receive health services, including oral PrEP. However, these are few and mainly located within hospitals and community centers in urban areas.

There are opportunities to simplify PrEP delivery and increase efficiencies in the PrEP program, for the benefit of both providers and PrEP users. Long waiting times and frequent refill visits are burdensome to PrEP clients. Considerations about frequency of PrEP visits are important, and should be tailored to PrEP users. A study conducted to examine uptake and adherence of PrEP among 15-19-year-old adolescents in South Africa (Pluspills) found that when refill visits increased from monthly to three-monthly, there was a reduction in PrEP continuation, however HIV uninfected persons in HIV serodiscordant partnerships within the Partners Scale-Up project in Kenya preferred less frequent visits.[177,178]

Increasing community awareness and demand creation

Community awareness of PrEP is necessary to ensure increased uptake and continued use of PrEP, reduce stigma and develop community acceptance of PrEP for HIV prevention. Indeed, young women in South Africa reported that if their community and neighbors were aware of PrEP, their usage would be easier.[179]

Various approaches have been utilized to increase PrEP awareness. Mass media is an effective tool as it reaches many people over a short period of time, but it is expensive to sustain. The Kenyan program had radio and television spots around the launch of the program and estimated a reach of over 11 million out of the 47 million people in the country.[17] Within health facilities, posters and other information material placed at waiting bays in out-patient departments, HIV care clinics, reproductive health clinics and clinics that provide services for key populations inform about availability of PrEP as an additional HIV prevention intervention. Lay health providers, (i.e., members of the

community who have received some training to promote health or to carry out some health-care services, but are not health-care professionals) also conduct PrEP health talks at hospital waiting bays, and in this way, educate clients seeking services at health facilities. Within communities, use of peer educators to increase PrEP knowledge and uptake has been successful with adolescent girls and young women, female sex workers and men who have sex with men.[96] In Kenya, for instance trained peer educators provided with brochures and other PrEP information materials reached 2,600 FSW with PrEP information of whom 280 initiated PrEP over a 7-month period. The HPTN 082 study, which had very high PrEP uptake employed innovative and youth-friendly print media, videos and community dialogues to inform communities about oral PrEP.[133] PrEP messaging and information should be directed at the general population, rather than calling out key populations in order to normalize use and provide a supportive environment, and not stigmatize those willing to use it. Additionally, such messaging should be positive, empowering and gain-framed rather than emphasize HIV risk.[180] These lessons learned, particularly about how to frame prevention for a health population, may be translatable to other settings and other infectious diseases.

Opportunities for PrEP programs in Africa

While PrEP initiations across African countries are promising, there is need to consider additional innovative strategies that can be employed in order to expand PrEP delivery to meet those at highest risk. Some of the opportunities are discussed below (Table 2):

Improving PrEP access for all populations

Efforts have been made to provide PrEP in the community in order to increase accessibility and to “demedicalize” PrEP.[181] Mobile vans have been used in PrEP programs in South Africa and Kenya to provide services especially to AGYW, away from health facilities.[182] Peers have been used to provide education and refer PrEP eligible persons. Considerations should be made for task-shifting some of the roles conducted by health providers to peers and community health workers. Another potentially promising idea is to assess the feasibility of PrEP provision within community pharmacies, as has been tried in limited fashion in the US.[183] In addition, increasing the number and variety of access points for PrEP services within health facilities will likely improve access.

Improving convenience of PrEP delivery

Identifying and implementing ways in which PrEP delivery can be made more efficient and accessible is the next frontier for PrEP programs in Africa. ART programs have minimalized baseline tests and successfully implemented differentiated care approaches, ‘one-stop shop’ delivery models and task shifting to improve efficiency of ART delivery and reduce stigma and PrEP programs would do well to borrow from these.[39] HIV self-testing (HIVST) to serve as a source of persons to initiate PrEP and as a way to streamline (and make more infrequent) follow-up visits could offer privacy and convenience for PrEP users and reduced workload for providers.[184]

Improving PrEP continuation

Stigma has been cited by PrEP users as a barrier to effective continued use.[159] PrEP delivery in less stigmatized settings such as by community health workers and peers and in community pharmacies which are convenient and private may foster better continuation rates. SMS reminders have been effective in promoting high adherence and retention in ART programs and could be considered for PrEP.[185]

Amplifying number of health workers able to offer PrEP services

Innovative strategies that will allow more providers receive PrEP training in a cost-effective manner are needed. Possible training approaches may include facility-based modular trainings and internet-based approaches.[35,186,187] On-job PrEP trainings have been conducted by supervisors and/or clinical PrEP champions.

Conclusions:

PrEP programs have been embraced in Africa and people at risk of acquiring HIV, once informed, are seeking PrEP services when availed. Programs have just begun and are expected to grow, resulting in increased PrEP uptake and continuation among those at risk in order to attain impactful coverage that will meet HIV prevention goals for the region. Countries may be called upon to make delivery simple and efficient in order to keep providers engaged and users motivated to benefit from PrEP services.

Funding

This work was supported by US National Institutes of Health under grants R01 MH095507 and P30 AI027757 and the Bill & Melinda Gates Foundation under grant OPP1056051.

Competing interests

EMI and JMB have been part of studies with study drug donated by Gilead Sciences. JMB has served as an advisor for Gilead Sciences, Merck, and Janssen. The authors have no other competing interests.

Table 5: Summary of select PrEP trials, demonstration projects, implementation projects and national programs across Africa

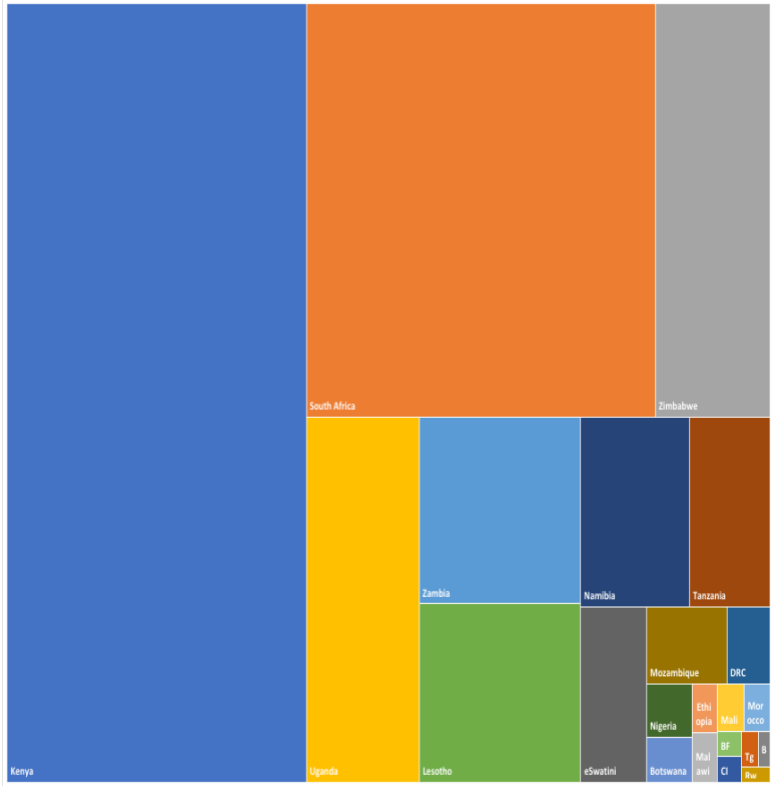
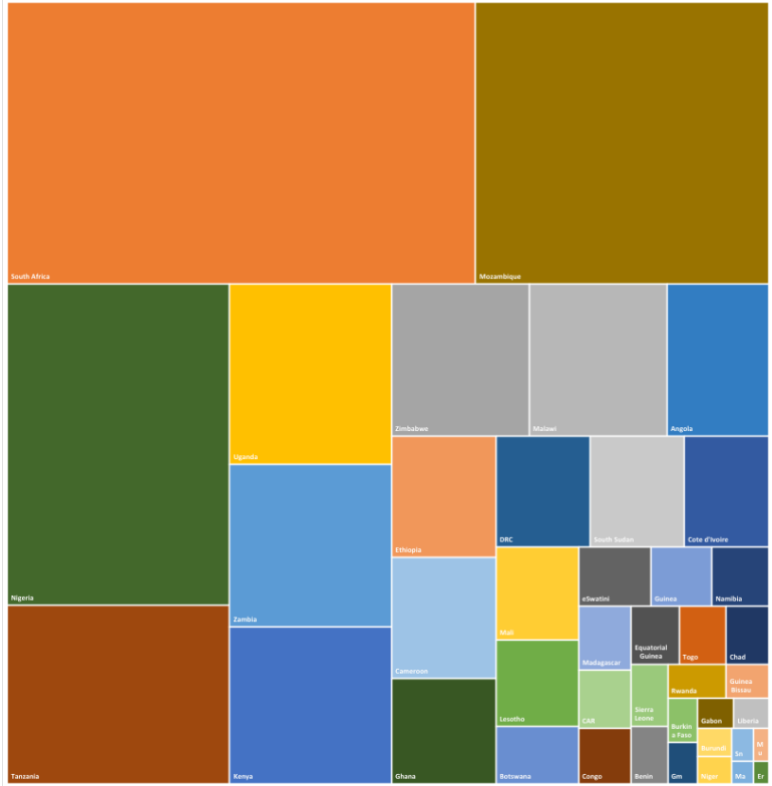
Population	Study Design	Study (Country)	Key Findings
HIV serodiscordant couples	Randomized Trial	Partners PrEP Study[3] *(Kenya & Uganda)*	• PrEP reduced risk of HIV acquisition by HIV uninfected men and women by 67-75% compared to placebo and by ≥90% among adherent individuals. • Both TDF and FTC/TDF were effective PrEP regimens.[188] • PrEP was safe, with few side effects, no evidence for serious adverse events, limited toxicities, and very limited risk of development of antiretroviral resistance. • No adverse interactions with contraception or conception; no evidence of adverse pregnancy or infant effects when used in the periconception period.[137,189]
	Demonstration Project	Partners Demonstration Project[8,115] *(Kenya & Uganda)*	• Integrated delivery of time-limited PrEP until sustained ART use HIV serodiscordant couples was associated with high uptake and adherence, and resulted in near elimination of HIV transmission (96% reduction compared to expected HIV incidence).

			• High safety in an open-label context; strong evidence for limited renal function monitoring in healthy populations.[190] • Qualitative work suggested high acceptability of PrEP in this population, including reduced anxiety and increased relationship trust.[122] • Able to be safely used throughout pregnancy.[191]
		Nigeria PrEP Demonstration Project[114] *(Nigeria)*	• PrEP uptake was high among screened couples, most of whom desired fertility.
	Implementation and Scale up	Partners Scale-Up Project[21,125] *(Kenya)*	• High PrEP uptake and use among people continuing PrEP in public health facilities.
Adolescent girls and young women	Randomized Trials	VOICE and FEM-PrEP[6,129] *(South Africa, Uganda, Zimbabwe, Kenya, Tanzania)*	• Very low adherence in placebo-controlled trials, driven in part by suspicion of using an unproven product.[192]
		HPTN 067/ADAPT Trial[132] *(South Africa)*	• Daily dosing of PrEP resulted in higher coverage of sex events and increased adherence to the regimen, compared to either time-driven or event-driven dosing.
	Demonstration Project	HPTN 082[133] *(South Africa & Zimbabwe)*	• There was high uptake of PrEP, although modest continuation through one year. • Drug level feedback, delayed by 1-2 months from sample collection, had no effect on PrEP adherence.

			• HIV incidence was substantially lower than anticipated (only 1% per year vs. expected 4-5% or more), arguably suggesting women took PrEP during periods of greatest risk.
		Introducing PrEP in Combination prevention (IPCP)[152] (*Kenya*)	• Close to 90% of eligible AGYW initiated PrEP but less than a third attended the scheduled month 1 visit.
		PlusPills[177] *(South Africa)*	• PrEP was safe and tolerable. • Usage decreased and adherence diminished when visits became less frequent. • STI diagnosis was high at baseline and remained high throughout.
		Feasibility, Acceptability, and Adherence with Short-Term HIV PrEP in Female Sexual Partners of Migrant Miners[134] *(Mozambique)*	• 97% of female partners of migrant workers initiated PrEP • Three quarters of women had detectable tenofovir diphosphate and 42% had levels consistent with ≥4 pills/wk at 6 weeks of follow up.
	Implementation and Scale up	Jilinde Project[193] *(Kenya)*	• Slow uptake of PrEP among young girls aged 15-19 years in the first year of the project.
		PrEP Implementation for Young Women and Adolescents (PrIYA) [138,142] *(Kenya)*	• 20% of women screened in family planning and maternal and child health clinics initiated PrEP. • About 50% had at least one refill visit.

		Zambian PrEP Program[141] *(Zambia)*	• 35% of those initiating PrEP in the first year of the program were young women aged 15-24 years.
Female sex workers	Demonstration Project	SAPPHIRE[150] *(Zimbabwe)*	• 38% of those screened for eligibility and offered PrEP initiated • Over 80% of those initiating returned for at least one visit.
		Benin Demonstration Study[151] *(Benin)*	• About 90% of eligible FSW initiated PrEP with close to half retained at the end of mean follow up time of 1 year.
		Introducing PrEP in Combination prevention (IPCP)[152] (*Kenya*)	• Two thirds of eligible FSW initiated PrEP and 60% of these attended the scheduled month 1 visit.
	Implementation and Scale up	South African PrEP Program[153] *(South Africa)*	• In the first two years of the program, over 4,000 FSW had initiated PrEP
		Jilinde Project[143] *(Kenya)*	• High uptake within the first eighteen months, with 60% of all initiating PrEP being FSW.
Men who have sex with men	Randomized Trial	Trial of an intermittent PrEP regimen among Kenyan MSM[158] *(Kenya)*	• Adherence to PrEP was higher among those assigned daily dosing compared to intermittent dosing.
	Demonstration Project	Introducing PrEP in Combination prevention (IPCP)[152] (*Kenya*)	• About three-quarters of eligible MSM initiated PrEP. Of these less than half attended their scheduled month 1 visit.

	Implementation and Scale Up	Jilinde[143] *(Kenya)*	• High interest and uptake within the first eighteen months, with 20% of all initiating PrEP being MSM.
		Zambian PrEP Program[141] *(Zambia)*	• Of 3,600 initiating PrEP in the first year of the national program, 100 are MSM.

Fig 10a: PrEP uptake in Africa, by country, October 2019	Fig 10b: New HIV infections in Africa, by country in 2018
	

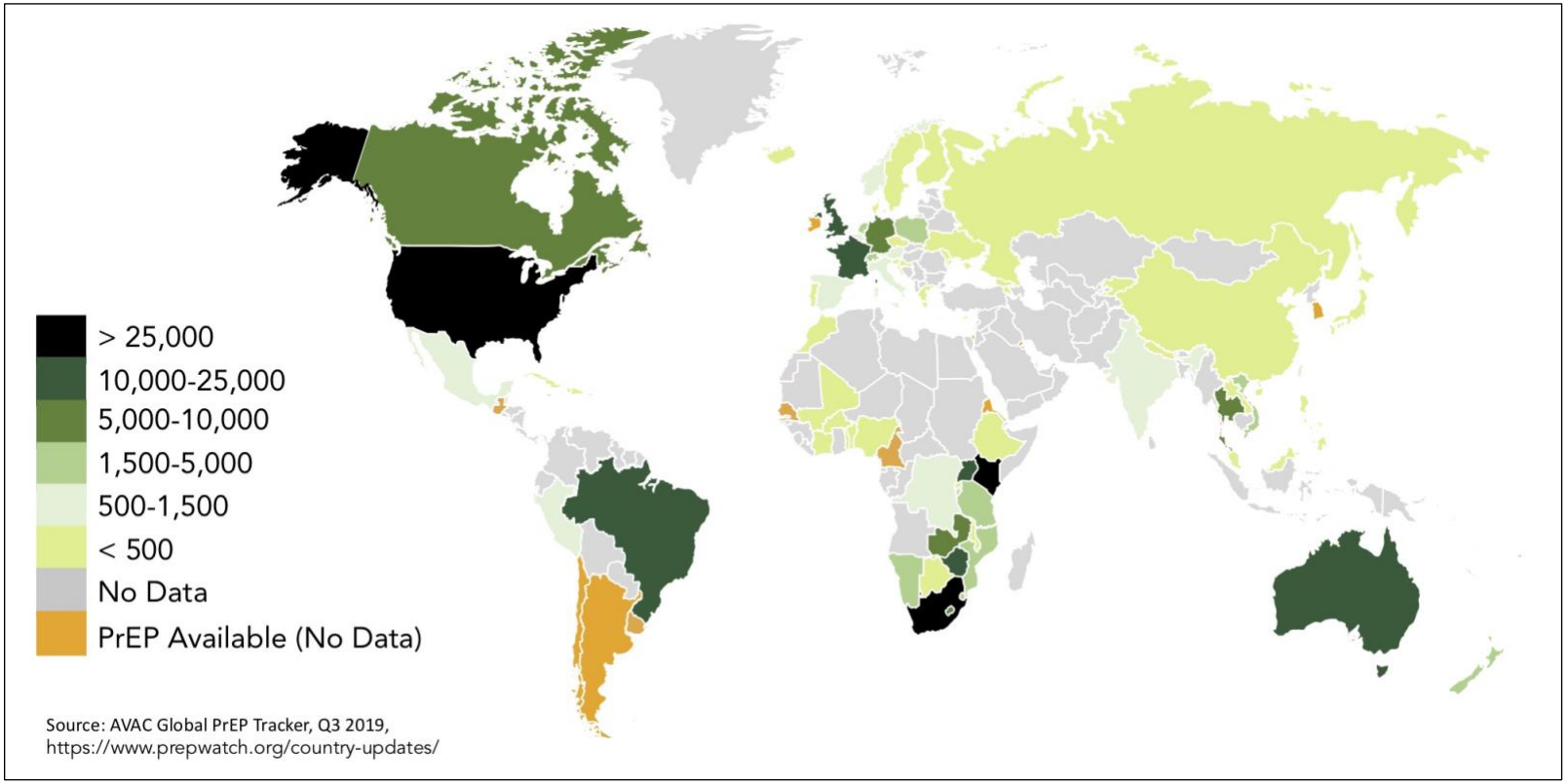
Legend:

Fig 1a: As of October 2019, the estimated number of persons who have initiated PrEP in Africa is between 136,150 and 144,050. The size of the rectangle in the figure is proportional to the number of persons ever initiating PrEP in the relevant country. *Source: PrEPWatch: Global PrEP Tracker*[110].

Fig 1b: The size of the rectangle is proportional to the number of new HIV infections in the relevant country in 2018. *Source: UNAIDS Data 2019*[104]

Abbreviations; Bn: Benin, BF: Burkina Faso, CAR: Central African Republic, CI: Cote D'Ivoire, DRC: Democratic Republic of Congo, Er: Eritrea, Gm: Gambia, Ma: Morocco, Mu: Mauritius; Rw: Rwanda, Sn: Senegal, Tg: Togo

Figure 11: PrEP Initiations by Country, October 2019



Source: *https://www.avac.org/sites/default/files/infographics/Oral_PrEP_Initiations_Global_Oct2019.jpg*

Chapter 6: Discussion

The work included in this dissertation is the first of its kind, and evaluates the effectiveness of PrEP implementation and integration in public HIV care clinics in Kenya. It contributes to a better understanding of a successful model of PrEP service delivery in Africa. This model entails training health providers on the PrEP curriculum and following up with technical assistance activities to provide mentorship to providers as they begin PrEP implementation. PrEP services within the clinics are provided by Ministry of Health staff using existing infrastructure.

The Partners Scale-Up Project, was a step wedge cluster randomized trial of PrEP integration in public health HIV care clinics that evaluated impact of this model of PrEP service delivery using implementation science methods.[21]

In chapter 2, we demonstrated that integration of PrEP services in public HIV clinics is a feasible, successful, and sustainable model of PrEP delivery. We report a sustained high monthly uptake of PrEP and high adherence among those who continued to take PrEP. Almost all tested samples had evidence of TDF/FTC. PrEP use may have been aligned to risk. Individuals with high HIV risk at baseline were more likely to continue use and those discontinuing PrEP reported reasons related to perception of reduced HIV risk including partner viral suppression and realization of conception. PrEP services were delivered with high fidelity and there were very low rates of HIV acquisition observed.

In chapter 3, using qualitative methods we examined summary technical reports and analyzed key informant interviews and identified clinic level adaptations to activities outlined in PrEP implementation guidelines and modifications made to existing service delivery practices to successfully incorporate PrEP services in public HIV clinics. Guided by the expanded framework for reporting adaptations and modifications (FRAME) we characterized identified adaptations.[31] We found that health providers made innovative adaptations to activities detailed in PrEP guidelines and instituted modifications to routine practices in order to simplify PrEP delivery processes for clients and to reduce service delivery barriers among health workers.

To expand PrEP delivery and amplify the number of health providers skilled to offer PrEP services in public health facilities, we designed and implemented an innovative on-site modular training approach. Training modules could be covered in two consecutive days or be broken across several days enabling flexibility to accommodate health provider work schedules. Using this approach, we provided PrEP training for more than 2,000 health providers in >100 health facilities, as reported in Chapter 4. We found that this low-cost training approach was accepted by health providers, resulted in knowledge gain among all cadres and was followed by sustained PrEP initiations in participating HIV clinics. On-site modular training facilitated many providers from the same facility to be trained together enabling open discussions that addressed facility-level challenges of PrEP delivery.

In chapter 5, we provide a summary of the status of PrEP roll out in Africa and detail lessons learned from early PrEP implementation. There has been high interest in PrEP services by all populations at risk of HIV acquisition but continuation is challenging. We highlight challenges to introduction of PrEP including identifying high risk individuals who might benefit from PrEP, combatting stigma related to being at risk of HIV, identifying accessible service delivery points for various populations and low community awareness of PrEP. We also suggest innovative ways to offer PrEP services efficiently such as community-based services, incorporate HIV self-testing and 'one-stop shopping' models.

Understanding the determinants of successful integration of PrEP in public HIV care clinics

Public HIV care clinics throughout sub-Sahara Africa are severely under resourced, overburdened and have marked inefficiencies in the delivery of health care.[194 195] However, they provide health services for the majority of the population and are therefore suited as a PrEP delivery avenue that may be sustainable and can be scaled up to attain maximal public health impact of HIV prevention.[39,196] We found that delivery of PrEP services integrated in public HIV care clinics was successful. Several factors may explain this success.

First, public HIV care clinics have a ready PrEP-eligible population. Partners of people living with HIV receive HIV prevention services including condoms and regular HIV testing at public HIV care clinics. They are also aware of their high risk of acquiring HIV

and hence more willing to take up PrEP.[119,197] This makes them a 'low-lying fruit' with whom to begin PrEP implementation, understand delivery and then expand to other populations.[198] Additionally, HIV serodiscordant couples are readily accepted as a population in need of PrEP, unlike other populations where there is moral judgement with PrEP use being associated with increased promiscuity.[199,200] In this project, the majority of those initiating PrEP reported having a HIV positive sex partner. However, it was interesting that 16% of PrEP initiations were among other populations, suggesting high demand for PrEP among other populations, making them seek services at a delivery point that is challenging to access for those not in HIV serodiscordant partnerships.

Second, health providers were eager to offer PrEP services. The Consolidated Framework for Implementation Research (CFIR), details that an intervention is more likely to be implemented when an organization (health facility) knows and prioritizes the needs of its patients.[30] Health providers have been taking care of HIV serodiscordant couples and have seen them attempt to achieve conception thereby increasing their risk of HIV transmission.[201-203] They desperately wanted an intervention they can offer HIV serodiscordant couples, especially those desiring conception,[204,205] and this demand may have facilitated PrEP integration into their routine services. In addition, health providers in public HIV care clinics know how to counsel, initiate and follow up persons on antiretroviral medications. They have done this successfully in HIV treatment programs.[206] Upon training, they grasped new concepts related to PrEP implementation with ease and begun to identify and offer services to at risk people, without additional

resources, staffing or infrastructure.[44] Health providers in public HIV care clinics in Africa frequently institute adaptations and modifications to help accommodate the increasing number of people living with HIV seeking services.[27] For the PrEP program they leveraged their experience working in these clinics to institute adaptations, similar to those in HIV treatment programs, in order to make the new PrEP program fit.[39,207] Some of these adaptions included longer refill times, initiating PrEP without creatinine testing and fast tracking. We found that clinics that implemented some of these adaptations also had higher mean monthly PrEP initiation and continuation rates, compared to those that did not. During the COVID pandemic, additional adaptations were observed including use of HIV self-testing to maintain social distancing, consultations via telephone or WhatsApp platforms and use of couriers to deliver PrEP. One shortcoming of working with health workers in public health facilities to provide PrEP counselling and education is that they may conflate PrEP use messaging and ART messaging, often requiring people not to interrupt PrEP use yet while HIV treatment requires life-long adherence, HIV prevention permits periodic use.[86] This conflation may be a deterrent to PrEP uptake and to cycling back into PrEP services as seasons of risk change.

Third, the policy environment in Kenya was conducive for PrEP introduction and implementation. Kenya has been at the forefront implementing highly effective HIV prevention interventions at scale, including immediate antiretroviral therapy to all persons living with HIV, voluntary medical male circumcision, prevention of mother-to-child transmission services and large-scale HIV testing programs. In 2013, The Kenya

Ministry of Health developed the HIV Prevention Revolution Road Map: Count Down to 2030, a national plan to drive new HIV-1 infections towards zero.[208] This document paved the way for PrEP introduction as it called for introduction of high-impact, evidence-based HIV prevention interventions. Soon after the WHO recommendation to offer PrEP to those with substantial HIV risk, Kenya revised her guidelines and included oral PrEP to be used in combination with existing interventions for HIV prevention.[14,15] The National AIDS and STI Control Program (NASCOP) set up coordination structures, including the PrEP technical working group that laid out the implementation framework.[16,17] The technical working group was mandated to provide strategic direction and oversight for the implementation of PrEP in Kenya in line with the health sector policies. Additionally, the national PrEP program was launched at a well-publicized, colorful ceremony officiated by the Minister of health and attended by other national and international stakeholders in HIV prevention. This demonstration of the government commitment and engagement forestalled barriers to PrEP introduction and implementation in public health facilities.[30]

Fourth, the involvement of HIV prevention researchers was essential. Key randomized clinical trials to establish safety and efficacy of oral PrEP were conducted in Kenya. These included the Partners PrEP Study among HIV serodiscordant couples[3], FEM-PrEP among women[6] and an IAVI-led trial among men who have sex with men and female sex workers.[158] These were then followed by several demonstration projects among different at risk populations.[115,209] Researchers engaged stakeholders, including providers in public health facilities where research participants were recruited,

throughout the conduct of these studies and provided results when the studies ended. Thus, there was awareness of PrEP safety and efficacy among national level HIV prevention managers even before PrEP became policy. It is likely that there was reduced resistance to PrEP implementation because some of the landmark trials were conducted in Kenya.[210,211] As members of the PrEP technical working group, HIV prevention researchers were also involved in the development of the revised guidelines and the PrEP implementation framework, where they provided guidance and clarified PrEP delivery concerns that stakeholders had.[15,16] Importantly, investigators and members of the clinical teams that conducted the Partners PrEP Study and the Partners Demonstration Project went on to support PrEP implementation within the Partners Scale-Up Project.[21] They trained health workers on PrEP delivery, shared their experiences acquired during the clinical trials and provided technical assistance where they mentored providers in public health facilities. As implementation begun, investigators shared early lessons with the technical working group, at national, regional and international meetings and through publications.[42,207,212-215] Sharing lessons early enabled the national program to understand PrEP implementation and provide support for facilities to continue implementation. A critical role provided by the researchers was obtaining funding to catalyze early PrEP implementation and function as a 'learning-laboratory' for PrEP implementation. Research activities drove the pace of scale-up in public health facilities. Thus, HIV prevention researchers and their teams served as external change agents i.e., 'individuals affiliated with an entity outside the public health facilities, who formally influenced and facilitated PrEP implementation in a desirable direction'.[30]

Ultimately, the public health impact of PrEP on the HIV epidemic in Africa will be attained only when PrEP services are offered at venues that are acceptable and accessible to those who need it most and are delivered in an efficient manner, that addresses barriers to PrEP uptake and continuation.[38] Public HIV care clinics may not be an acceptable venue for all members of all populations such as adolescent girls and young women or key populations, including men who have sex with men and sex workers, and other venues should be explored. Feasibility of PrEP delivery in family planning and ante-natal clinics in Kenya has already been demonstrated[142,216,217] and a large PrEP implementation program in Kenya has successfully provided PrEP for key populations in drop-in-centres.[218] In South Africa and Kenya, another real-world implementation program is evaluating PrEP delivery for young women in family planning clinics, youth friendly clinics and mobile clinics.[219] Innovative approaches that are convenient, confidential and away from public health facilities such as home-based delivery, PrEP delivery by peers and PrEP provision at community pharmacies are under evaluation.[220-222]

Next steps for policy

PrEP delivery at scale is required to end the HIV epidemic. Recently completed population-based universal test and treat trials failed to achieve HIV elimination targets despite achieving high population-level viral suppression rates.[223-226] This suggests that in addition to HIV treatment, HIV prevention interventions, including oral PrEP are necessary to eliminate HIV.[227] In developed countries where PrEP has been delivered

at scale alongside antiretroviral treatment new HIV infections have declined substantially.[228,229]

This dissertation provides evidence that it is feasible to integrate and scale up PrEP service delivery in high volume public HIV care clinics. In addition, we demonstrate a low-cost, acceptable approach with which to build the capacity of health providers. It is important that PrEP services are expanded to many more public HIV clinics in Kenya, especially those found in low-tier facilities and in rural areas. This will improve PrEP access for many more people in need of HIV prevention. In addition, it will pave the way for new PrEP options including rings and injectable PrEP.[169]

Most of PrEP in Kenya is availed through public health facilities. However, it is imperative that PrEP services are scaled out i.e., a deliberate effort to broaden the delivery of PrEP to venues that are accessible and acceptable to other high-risk populations.[230] Research has demonstrated feasibility of implementation in drop-in-centers, youth friendly clinics, family planning clinics and maternal and child health clinics.[142,216,218] The next step is to expand delivery in these spaces. Findings reported in this dissertation including some adaptations and training approaches may be applicable during this expansion.

More research is needed to evaluate the impact of the observed adaptations on PrEP delivery. Task shifting, PrEP provision in clinical rooms and fast-tracked delivery are

adaptations that could be rigorously evaluated and if proven effective could be incorporated in PrEP delivery guidelines.

Conclusion

This dissertation demonstrates that provision of PrEP services integrated in public HIV care clinics in Africa is feasible. Our findings inform Kenya's national scale up of PrEP and other countries in the African region that are beginning implementation of national PrEP programs.

VITA

Elizabeth Irungu completed her PhD in Implementation Science in the Department of Global Health at the University of Washington in May 2021. She obtained her medical training from University of Nairobi in Kenya, and her MPH from University of Washington, Seattle. She worked as a medical officer in several public health facilities in central Kenya, before moving to Partners in Health Research and Development (PHRD) where she has been a research scientist for the last 14 years. For the work described in this dissertation, Elizabeth led the in-country activities of the Partners Scale-Up Project, including coordinating training and technical assistance, over-seeing data collection, conducting data analysis and developing the manuscripts. Her research interests focus on HIV prevention among HIV serodiscordant couples and other at-risk populations and evaluating strategies to foster uptake and implementation of novel HIV prevention interventions, including oral PrEP.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS. UNAIDS DATA 2020. Geneva, Switzerland, 2020.

2. Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. *Curr HIV/AIDS Rep* 2011; **8**(1): 62-72.

3. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *New England Journal of Medicine* 2012; **367**(5): 399-410.

4. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet* 2013; **381**(9883): 2083-90.

5. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *New England Journal of Medicine* 2012; **367**(5): 423-34.

6. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367**(5): 411-22.

7. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine* 2010; **363**(27): 2587-99.

8. Baeten JM, Heffron R, Kidoguchi L, et al. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1-Serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. *PLOS Medicine* 2016; **13**(8): e1002099.

9. Molina J-M, Capitant C, Spire B, et al. On Demand PrEP With Oral TDF-FTC in MSM: Results of the ANRS Ipergay Trial. CROI. Seattle, Washington; 2015.

10. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2015.

11. Celum C, Mgodi N, Bekker L-G, Hosek S, Donnell D, Delany-Moretlwe S. PrEP use in young African women in HPTN 082: Effect of drug level feedback. 10th IAS Conference on HIV Science; 2019; Mexico City; 2019.

12. PrEPWatch. Global PrEP Initiation Tracker. 2018. https://www.prepwatch.org/country-updates/.

13. Irungu EM, Baeten JM. PrEP rollout in Africa: status and opportunity. *Nat Med* 2020; **26**(5): 655-64.

14. World Health Organization. Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015.

15. National AIDS and STI Control Programme (NASCOP). Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infections in Kenya. 2016.

16. National AIDS and STI Control Programme (NASCOP). Framework for the Implementation of Pre-exposure Prophylaxis of HIV in Kenya. Nairobi, Kenya, 2017.

17. Masyuko S, Mukui I, Njathi O, et al. Pre-exposure prophylaxis rollout in a national public sector program: the Kenyan case study. *Sex Health* 2018; **15**(6): 578-86.

18. Einterz RM, Kimaiyo S, Mengech HN, et al. Responding to the HIV pandemic: the power of an academic medical partnership. *Acad Med* 2007; **82**(8): 812-8.

19. U.S. Centers for Diseases Control and Kenya Ministry of Health. Report of a Cost Study of HIV Treatment Programs in Kenya. Atlanta, GA (USA) and Nairobi, Kenya, 2013.

20. (NASCOP) NAaSCP. National HIV Programme Key Highlights Bulletin (2017-2018) https://www.nascop.or.ke/strategic-information-downloads/. 2018.

21. Mugwanya KK, Irungu E, Bukusi E, et al. Scale up of PrEP integrated in public health HIV care clinics: a protocol for a stepped-wedge cluster-randomized rollout in Kenya. *Implementation Science* 2018; **13**(1): 118.

22. Mudiope P, Musingye E, Makumbi CO, et al. Greater involvement of HIV-infected peer-mothers in provision of reproductive health services as "family planning champions" increases referrals and uptake of family planning among HIV-infected mothers. *BMC Health Serv Res* 2017; **17**(1): 444.

23. Oldfield BJ, Munoz N, Boshnack N, et al. "No more falling through the cracks": A qualitative study to inform measurement of integration of care of HIV and opioid use disorder. *Journal of substance abuse treatment* 2019; **97**: 28-40.

24. Oxner A, Kongpakpaisarn K, Hudey S, et al. Bundling HIV and TB Care at a District-Level Center in Sierra Leone: A high-yield method for diagnosing co-infection with TB and antiretroviral treatment failure among people living with HIV. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2019; **82**: 124-8.

25. Rodriguez V, Lester D, Connelly-Flores A, Barsanti FA, Hernandez P. Integrating Routine HIV Screening in the New York City Community Health Center Collaborative. *Public health reports (Washington, DC : 1974)* 2016; **131 Suppl 1**: 11-20.

26. Vorkas CK, Tweya H, Mzinganjira D, et al. Practices to improve identification of adult antiretroviral therapy failure at the Lighthouse Trust clinic in Lilongwe, Malawi. *Trop Med Int Health* 2012; **17**(2): 169-76.

27. Zakumumpa H, Bennett S, Ssengooba F. Modifications to ART service delivery models by health facilities in Uganda in promotion of intervention sustainability: a mixed methods study. *Implement Sci* 2017; **12**(1): 45.

28. Dusenbury L, Brannigan R, Falco M, Hansen WB. A review of research on fidelity of implementation: implications for drug abuse prevention in school settings. *Health education research* 2003; **18**(2): 237-56.

29. Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. *Implement Sci* 2007; **2**: 40.

30. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implementation Science* 2009; **4**: 50.

31. Wiltsey Stirman S, Baumann AA, Miller CJ. The FRAME: an expanded framework for reporting adaptations and modifications to evidence-based interventions. *Implement Sci* 2019; **14**(1): 58.

32. Skolnik AA, Bokhour BG, Gifford AL, Wilson BM, Van Epps P. Roadblocks to PrEP: What Medical Records Reveal About Access to HIV Pre-exposure Prophylaxis. *Journal of general internal medicine* 2019.

33. Petroll AE, Walsh JL, Owczarzak JL, McAuliffe TL, Bogart LM, Kelly JA. PrEP Awareness, Familiarity, Comfort, and Prescribing Experience among US Primary Care Providers and HIV Specialists. *AIDS and Behaviour* 2017; **21**(5): 1256-67.

34. Krakower DS, Oldenburg CE, Mitty JA, et al. Knowledge, Beliefs and Practices Regarding Antiretroviral Medications for HIV Prevention: Results from a Survey of Healthcare Providers in New England. *PLOS One* 2015; **10**(7): e0132398.

35. Wood BR, Mann MS, Martinez-Paz N, et al. Project ECHO: telementoring to educate and support prescribing of HIV pre-exposure prophylaxis by community medical providers. *Sexual health* 2018; **15**(6): 601-5.

36. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *Aids* 2016; **30**(12): 1973-83.

37. Mayer KH, Chan PA, R RP, Flash CA, Krakower DS. Evolving Models and Ongoing Challenges for HIV Preexposure Prophylaxis Implementation in the United States. *J Acquir Immune Defic Syndr* 2018; **77**(2): 119-27.

38. Sullivan PS, Siegler AJ. Getting pre-exposure prophylaxis (PrEP) to the people: opportunities, challenges and emerging models of PrEP implementation. *Sex Health* 2018; **15**(6): 522-7.

39. O'Malley G, Barnabee G, Mugwanya K. Scaling-up PrEP Delivery in Sub-Saharan Africa: What Can We Learn from the Scale-up of ART? *Curr HIV/AIDS Rep* 2019; **16**(2): 141-50.

40. Mugo NR, Ngure K, Kiragu M, Irungu E, Kilonzo N. The preexposure prophylaxis revolution; from clinical trials to programmatic implementation. *Curr Opin HIV AIDS* 2016; **11**(1): 80-6.

41. National AIDS and STI Control Programme (NASCOP). Preliminary KENPHIA 2018 Report. Nairobi: NASCOP, 2020.

42. Odoyo JB, Morton JF, Ngure K, et al. Integrating PrEP into HIV care clinics could improve partner testing services and reinforce mutual support among couples: provider views from a PrEP implementation project in Kenya. *J Int AIDS Soc* 2019; **22 Suppl 3**: e25303.

43. National AIDS Control Council. Kenya HIV Estimates Report 2018. Nairobi: Ministry of Health, Kenya, 2018.

44. Irungu EM, Ngure K, Mugwanya K, et al. Training health care providers to provide PrEP for HIV serodiscordant couples attending public health facilities in Kenya. *Glob Public Health* 2019: 1-11.

45. Zheng JH, Rower C, McAllister K, et al. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. *J Pharm Biomed Anal* 2016; **122**: 16-20.

46. Anderson PL, Liu AY, Castillo-Mancilla JR, et al. Intracellular Tenofovir-Diphosphate and Emtricitabine-Triphosphate in Dried Blood Spots following Directly Observed Therapy. *Antimicrob Agents Chemother* 2018; **62**(1).

47. Kahle EM, Hughes JP, Lingappa JR, et al. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. *J Acquir Immune Defic Syndr* 2013; **62**(3): 339-47.

48. Haberer JE, Bangsberg DR, Baeten JM, et al. Defining success with HIV pre-exposure prophylaxis: a prevention-effective adherence paradigm. *Aids* 2015; **29**(11): 1277-85.

49. WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 3: Counsellors. Geneva: World Health Organization, 2017.

50. WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 1 : Clinical. Geneva: World Health Organization, 2017.

51. Koss CA, Charlebois ED, Ayieko J, et al. Uptake, engagement, and adherence to pre-exposure prophylaxis offered after population HIV testing in rural Kenya and Uganda: 72-week interim analysis of observational data from the SEARCH study. *Lancet HIV* 2020; **7**(4): e249-e61.

52. Krakower D, Mayer KH. Engaging healthcare providers to implement HIV pre-exposure prophylaxis. *Curr Opin HIV AIDS* 2012; **7**(6): 593-9.

53. Zanolini A, Sikombe K, Sikazwe I, et al. Understanding preferences for HIV care and treatment in Zambia: Evidence from a discrete choice experiment among patients who have been lost to follow-up. *PLoS Med* 2018; **15**(8): e1002636.

54. Krakower D, Ware N, Mitty JA, Maloney K, Mayer KH. HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care settings: a qualitative study. *AIDS Behav* 2014; **18**(9): 1712-21.

55. Wagenaar BH, Sherr K, Fernandes Q, Wagenaar AC. Using routine health information systems for well-designed health evaluations in low- and middle-income countries. *Health Policy Plan* 2016; **31**(1): 129-35.

56. Ahmed N, Pike C, Bekker LG. Scaling up pre-exposure prophylaxis in sub-Saharan Africa. *Curr Opin Infect Dis* 2019; **32**(1): 24-30.

57. Celum CL, Delany-Moretlwe S, Baeten JM, et al. HIV pre-exposure prophylaxis for adolescent girls and young women in Africa: from efficacy trials to delivery. *J Int AIDS Soc* 2019; **22 Suppl 4**(Suppl Suppl 4): e25298.

58. Sullivan PS, Mena L, Elopre L, Siegler AJ. Implementation Strategies to Increase PrEP Uptake in the South. *Curr HIV/AIDS Rep* 2019; **16**(4): 259-69.

59. Bazzi AR, Drainoni ML, Biancarelli DL, et al. Systematic review of HIV treatment adherence research among people who inject drugs in the United States and Canada: evidence to inform pre-exposure prophylaxis (PrEP) adherence interventions. *BMC Public Health* 2019; **19**(1): 31.

60. Mack N, Wong C, McKenna K, Lemons A, Odhiambo J, Agot K. Human Resource Challenges to Integrating HIV Pre-Exposure Prophylaxis (PrEP) into the Public Health System in Kenya: A Qualitative Study. *Afr J Reprod Health* 2015; **19**(1): 54-62.

61. Escoffery C, Lebow-Skelley E, Haardoerfer R, et al. A systematic review of adaptations of evidence-based public health interventions globally. *Implement Sci* 2018; **13**(1): 125.

62. Chambers DA, Norton WE. The Adaptome: Advancing the Science of Intervention Adaptation. *Am J Prev Med* 2016; **51**(4 Suppl 2): S124-31.

63. Lewis Kulzer J, Penner JA, Marima R, et al. Family model of HIV care and treatment: a retrospective study in Kenya. *J Int AIDS Soc* 2012; **15**(1): 8.

64. Odundo G, Ongadi P, Nyarango R, Lubembe E, Chanzu N. A Comprehensive Family Centered HIV Care and Support Centre at the Gertrude's Children's Hospital, Nairobi, Kenya. *Archives of Medicine* 2016; **8**(9).

65. Ministry of Health, National AIDS and STI Control Programme (NASCOP). Status on implementation of Oral Pre-exposure Prophylaxis for HIV in Kenya 2018. Nairobi, Kenya: NASCOP, 2018.

66. Ayieko J, Brown L, Anthierens S, et al. "Hurdles on the path to 90-90-90 and beyond": Qualitative analysis of barriers to engagement in HIV care among individuals in rural East Africa in the context of test-and-treat. *PLoS One* 2018; **13**(8): e0202990.

67. Nyato D, Nnko S, Komba A, et al. Facilitators and barriers to linkage to HIV care and treatment among female sex workers in a community-based HIV prevention intervention in Tanzania: A qualitative study. *PLoS One* 2019; **14**(11): e0219032.

68. Tomori C, Kennedy CE, Brahmbhatt H, et al. Barriers and facilitators of retention in HIV care and treatment services in Iringa, Tanzania: the importance of socioeconomic and sociocultural factors. *AIDS Care* 2014; **26**(7): 907-13.

69. Kwarisiima D, Kamya MR, Owaraganise A, et al. High rates of viral suppression in adults and children with high CD4+ counts using a streamlined ART delivery model in the SEARCH trial in rural Uganda and Kenya. *J Int AIDS Soc* 2017; **20**(Suppl 4): 21673.

70. Duncombe C, Rosenblum S, Hellmann N, et al. Reframing HIV care: putting people at the centre of antiretroviral delivery. *Trop Med Int Health* 2015; **20**(4): 430-47.

71. Pantelic M, Stegling C, Shackleton S, Restoy E. Power to participants: a call for person-centred HIV prevention services and research. *J Int AIDS Soc* 2018; **21 Suppl 7**(Suppl Suppl 7): e25167.

72. Burmen B, Owuor N, Mitei P. An assessment of staffing needs at a HIV clinic in a Western Kenya using the WHO workload indicators of staffing need WISN, 2011. *Hum Resour Health* 2017; **15**(1): 9.

73. Abejirinde IO, Ilozumba O, Marchal B, Zweekhorst M, Dieleman M. Mobile health and the performance of maternal health care workers in low- and middle-income countries: A realist review. *Int J Care Coord* 2018; **21**(3): 73-86.

74. Ledikwe JH, Kejelepula M, Maupo K, et al. Evaluation of a well-established task-shifting initiative: the lay counselor cadre in Botswana. *PLoS One* 2013; **8**(4): e61601.

75. World Health Organization. Task shifting : rational redistribution of tasks among health workforce teams : global recommendations and guidelines. Geneva, Switzerland, 2008.

76. Kapologwe N, Mahande M, Msuya SE. Provider-initiated HIV testing and counseling in Mbeya City, south-western Tanzania: knowledge and practice of health care providers. *Tanzan J Health Res* 2011; **13**(4): 95-100.

77. Ndwiga C, Abuya T, Mutemwa R, et al. Exploring experiences in peer mentoring as a strategy for capacity building in sexual reproductive health and HIV service integration in Kenya. *BMC Health Serv Res* 2014; **14**: 98.

78. Pinto RM, Witte SS, Filippone P, Choi CJ, Wall M. Interprofessional Collaboration and On-the-Job Training Improve Access to HIV Testing, HIV Primary Care, and Pre-Exposure Prophylaxis (PrEP). *AIDS Educ Prev* 2018; **30**(6): 474-89.

79. Operations Manual for Delivery of HIV Prevention, Care and Treatment at Primary Health Centres in High-Prevalence, Resource-Constrained Settings: Edition 1 for Fieldtesting and Country Adaptation. Geneva: World Health Organization; 2008.

80. Alamo ST, Wagner GJ, Sunday P, et al. Electronic medical records and same day patient tracing improves clinic efficiency and adherence to appointments in a community based HIV/AIDS care program, in Uganda. *AIDS Behav* 2012; **16**(2): 368-74.

81. Castelnuovo B, Kiragga A, Afayo V, et al. Implementation of provider-based electronic medical records and improvement of the quality of data in a large HIV program in Sub-Saharan Africa. *PLoS One* 2012; **7**(12): e51631.

82. Castro FG, Barrera M, Jr., Martinez CR, Jr. The cultural adaptation of prevention interventions: resolving tensions between fidelity and fit. *Prev Sci* 2004; **5**(1): 41-5.

83. Doyle K, Hungerford C. Adapting evidence-based interventions to accommodate cultural differences: where does this leave effectiveness? *Issues Ment Health Nurs* 2014; **35**(10): 739-44.

84. Rohrbach LA, Grana R, Sussman S, Valente TW. Type II translation: transporting prevention interventions from research to real-world settings. *Eval Health Prof* 2006; **29**(3): 302-33.

85. Stirman SW, Miller CJ, Toder K, Calloway A. Development of a framework and coding system for modifications and adaptations of evidence-based interventions. *Implement Sci* 2013; **8**: 65.

86. Venter WDF. Pre-exposure Prophylaxis: The Delivery Challenge. *Front Public Health* 2018; **6**: 188.

87. Krakower DS, Mayer KH. The role of healthcare providers in the roll out of preexposure prophylaxis. *Current Opinion in HIV and AIDS* 2016; **11**(1): 41-8.

88. Pinto RM, Berringer KR, Melendez R, Mmeje O. Improving PrEP Implementation Through Multilevel Interventions: A Synthesis of the Literature. *AIDS Behav* 2018; **22**(11): 3681-91.

89. Blumenthal J, Jain S, Krakower D, et al. Knowledge is Power! Increased Provider Knowledge Scores Regarding Pre-exposure Prophylaxis (PrEP) are Associated with Higher Rates of PrEP Prescription and Future Intent to Prescribe PrEP. *AIDS Behav* 2015; **19**(5): 802-10.

90. Castel AD, Feaster DJ, Tang W, et al. Understanding HIV Care Provider Attitudes Regarding Intentions to Prescribe PrEP. *J Acquir Immune Defic Syndr* 2015; **70**(5): 520-8.

91. Ministry of Health, National AIDS and STI Control Programme (NASCOP). A Report on Assessment of Health Facilities Providing Oral Pre-Exposure Prophylaxis for HIV in Kenya. Nairobi, Kenya: NASCOP, 2018.

92. Vassall A, Sweeney S, Kahn JG, et al. Reference Case for Estimating the Costs of Global Health Services and Interventions. . 2017.

93. MySalaryScale. New Civil Servants' Salary Structure in Kenya (https://www.mysalaryscale.com/blog/new-civil-servants-salary-structure-in-kenya/).

94. CurrencyConverter USD KES Historical Exchange Rate [Available from https://www.currency-converter.org.uk/currency-rates/historical/table/USD-KES.html.

95. Vanhamel J, Rotsaert A, Reyniers T, et al. The current landscape of pre-exposure prophylaxis service delivery models for HIV prevention: a scoping review. *BMC Health Serv Res* 2020; **20**(1): 704.

96. Medley A, Kennedy C, O'Reilly K, Sweat M. Effectiveness of peer education interventions for HIV prevention in developing countries: a systematic review and meta-analysis. *AIDS Educ Prev* 2009; **21**(3): 181-206.

97. Heller RF, Chongsuvivatwong V, Hailegeorgios S, et al. Capacity-building for public health: http://peoples-uni.org. *Bull World Health Organ* 2007; **85**(12): 930-4.

98. Irungu E, Sharma M, Maronga C, et al. The Incremental Cost of Delivering PrEP as a Bridge to ART for HIV Serodiscordant Couples in Public HIV Care Clinics in Kenya. *AIDS Research and Treatment* 2019; (5): 1-8.

99. Tani K, Exavery A, Baynes CD, et al. Unit cost analysis of training and deploying paid community health workers in three rural districts of Tanzania. *BMC Health Serv Res* 2016; **16**: 237.

100. Willcox M, LeFevre A, Mwebaza E, Nabukeera J, Conecker G, Johnson P. Cost analysis and provider preferences of low-dose, high-frequency approach to in-service training programs in Uganda. *J Glob Health* 2019; **9**(1): 010416.

101. Touger R, Wood BR. A Review of Telehealth Innovations for HIV Pre-Exposure Prophylaxis (PrEP). *Curr HIV/AIDS Rep* 2019; **16**(1): 113-9.

102. Clement ME, Seidelman J, Wu J, et al. An educational initiative in response to identified PrEP prescribing needs among PCPs in the Southern U.S. *AIDS Care* 2018; **30**(5): 650-5.

103. Capital Ka Cyrilliciriazova TK, Neduzhko OO, Kang Dufour M, Culyba RJ, Myers JJ. Evaluation of the effectiveness of HIV voluntary counseling and testing trainings for clinicians in the Odessa region of Ukraine. *AIDS Behav* 2014; **18 Suppl 1**: S89-95.

104. Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2019. Geneva, Switzerland, 2019.

105. UNAIDS. AIDSinfo. 17 December 2019 2019. http://aidsinfo.unaids.org/.

106. Mayer CM, Owaraganise A, Kabami J, et al. Distance to clinic is a barrier to PrEP uptake and visit attendance in a community in rural Uganda. *Journal of the International AIDS Society* 2019; **22**(4): e25276.

107. Centers for Disease Control and Prevention (CDC). Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. *MMWR Morbidity and mortality weekly report* 2011; **60**(3): 65-8.

108. Food and Drug Administration. FDA approves first drug for reducing the risk of sexually acquired HIV infection. *http://wwwfdagov/NewsEvents/Newsroom/PressAnnouncements/ucm312210htm* 2013.

109. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. . 2nd ed. Geneva; 2016.

110. AVAC. PrEPWatch. Global PrEP Tracker. https://www.prepwatch.org/country-updates/ (accessed 28 January 2020.

111. Organization WH. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. Recommendations for use in the context of demonstration projects. 2012.

112. Dunkle KL, Stephenson R, Karita E, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. *Lancet* 2008; **371**(9631): 2183-91.

113. Grabbe KL, Bunnell R. Reframing HIV prevention in sub-Saharan Africa using couple-centered approaches. *JAMA* 2010; **304**(3): 346-7.

114. Matthias A, Folayan M, Anenih J, et al. Nigerian pre-exposure prophylaxis (PrEP) study: sociodemographic profile and fertility desire among HIV-1 sero-discordant couples in Nigeria. *19th International Conference on AIDS and STI's in Africa* 2017.

115. Heffron R, Ngure K, Odoyo J, et al. Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa. *Gates Open Res* 2017; **1**: 3.

116. Irungu E, Heffron R, Mugo N, et al. Evaluation of a risk score to identify higher-risk HIV-1 serodiscordant couples for evaluation of Antiretroviral-based HIV-1 prevention interventions. *CUGH* 2014.

117. Pyra M, Brown ER, Haberer JE, et al. Patterns of Oral PrEP Adherence and HIV Risk Among Eastern African Women in HIV Serodiscordant Partnerships. *AIDS Behav* 2018; **22**(11): 3718-25.

118. Pyra M, Haberer JE, Heffron R, et al. Brief Report: PrEP Use During Periods of HIV Risk Among East African Women in Serodiscordant Relationships. *Journal of acquired immune deficiency syndromes (1999)* 2018; **77**(1): 41-5.

119. Ware NC, Wyatt MA, Haberer JE, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. *J Acquir Immune Defic Syndr* 2012; **59**(5): 463-8.

120. Nakku-Joloba E, Pisarski EE, Wyatt MA, et al. Beyond HIV prevention: everyday life priorities and demand for PrEP among Ugandan HIV serodiscordant couples. *Journal of the International AIDS Society* 2019; **22**(1): e25225.

121. Mack N, Evens EM, Tolley EE, et al. The importance of choice in the rollout of ARV-based prevention to user groups in Kenya and South Africa: a qualitative study. *Journal of the International AIDS Society* 2014; **17**(3 Suppl 2): 19157.

122. Ngure K, Heffron R, Curran K, et al. I Knew I Would Be Safer. Experiences of Kenyan HIV Serodiscordant Couples Soon After Pre-Exposure Prophylaxis (PrEP) Initiation. *AIDS Patient Care STDS* 2016; **30**(2): 78-83.

123. Acom CP. Mobile Health Approaches with Facility-based Care to Improve Access and Adherence to Pre-exposure Prophylaxis (PrEP) in Lango Region, Uganda. *20th ICASA International Conference on AIDS and STI's in Africa; 2 - 7 December* 2019.

124. OPTIONS. PrEP Learning Network Regional Workshop. 2019. https://www.prepwatch.org/wp-content/uploads/2019/11/WelcomeEnablingPolicyEnvironment_malawi_nov2019.pdf.

125. Irungu E, Mugwanya K, Bukusi E, et al. High PrEP use in African men and women continuing PrEP in public health HIV clinics. *Conference on Retroviruses and Opportunistic Infections (CROI)* 2019.

126. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. *Lancet (London, England)* 2019; **394**(10195): 303-13.

127. Celum CL, Delany-Moretlwe S, McConnell M, et al. Rethinking HIV prevention to prepare for oral PrEP implementation for young African women. *Journal of the International AIDS Society* 2015; **18**(4 Suppl 3): 20227.

128. Wekesah F, Nyakangi V, Onguss M, Njagi J, Bangha M. Comprehensive Sexuality Education in Sub-Saharan Africa. 2019.

129. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015; **372**(6): 509-18.

130. Stankevitz K, Schwartz K, Hoke T, et al. Reaching at-risk women for PrEP delivery: What can we learn from clinical trials in sub-Saharan Africa? *PLOS One* 2019; **14**(6): e0218556.

131. Henderson F, Taylor A, Chirwa L, et al. Characteristics and oral PrEP adherence in the TDF2 open-label extension in Botswana. *International AIDS Conference , 18-22 July* 2015.

132. Bekker LG, Roux S, Sebastien E, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. *Lancet HIV* 2018; **5**(2): e68-e78.

133. Celum C, Mgodi N, Bekker L-G, et al. PrEP adherence and effect of drug level feedback among young African women in HPTN 082. *International AIDS Society* 2019.

134. Lahuerta M, Zerbe A, Baggaley R, et al. Feasibility, Acceptability, and Adherence with Short-Term HIV Preexposure Prophylaxis in Female Sexual Partners of Migrant Miners in Mozambique. *Journal of acquired immune deficiency syndromes (1999)* 2017; **76**(4): 343-7.

135. Pintye J, Beima-Sofie KM, Makabong OP, et al. HIV-Uninfected Kenyan Adolescent and Young Women Share Perspectives on Using Preexposure Prophylaxis During Pregnancy. *AIDS patient care and STDs* 2018.

136. Govender E, Mansoor L, MacQueen K, Abdool Karim Q. Secrecy, empowerment and protection: positioning PrEP in KwaZulu-Natal, South Africa. *Culture, health & sexuality* 2017; **19**(11): 1268-85.

137. Matthews LT, Heffron R, Mugo NR, et al. High medication adherence during periconception periods among HIV-1-uninfected women participating in a clinical trial of

antiretroviral pre-exposure prophylaxis. *Journal of acquired immune deficiency syndromes (1999)* 2014; **67**(1): 91-7.

138. Kinuthia J, Pintye J, Abuna F, et al. Pre-exposure prophylaxis uptake and early continuation among pregnant and post-partum women within maternal and child health clinics in Kenya: results from an implementation programme. *Lancet HIV* 2019.

139. Heffron R, Thomson K, Celum C, et al. Fertility Intentions, Pregnancy, and Use of PrEP and ART for Safer Conception Among East African HIV Serodiscordant Couples. *AIDS Behav* 2018; **22**(6): 1758-65.

140. World Health Organization. Technical Brief: Preventing HIV during pregnancy and breastfeeding in the context of PrEP. 2017.

141. Claassen CW, Mumba D, Njelesani M, et al. First year of implementation of PrEP in Zambia: Service delivery roll-out and scale-up. *International AIDS Society* 2019.

142. Mugwanya KK, Pintye J, Kinuthia J, et al. Integrating preexposure prophylaxis delivery in routine family planning clinics: A feasibility programmatic evaluation in Kenya. *PLoS Med* 2019; **16**(9): e1002885.

143. Mutegi J, Ongwen P, Musau A, Wakhutu B, Curran K, Reed J. Characteristics of oral pre-exposure prophylaxis (PrEP) clients with periodic use in the Jilinde program, Kenya. *International AIDS Society* 2019.

144. Pyra MN, Haberer JE, Hasen N, Reed J, Mugo NR, Baeten JM. Global implementation of PrEP for HIV prevention: setting expectations for impact. *Journal of the International AIDS Society* 2019; **22**(8): e25370.

145. Joint United Nations Programme on HIV/AIDS (UNAIDS). The Gap Report: Sex workers. Geneva, Switzerland, 2014.

146. Mutagoma M, Samuel MS, Kayitesi C, et al. High HIV prevalence and associated risk factors among female sex workers in Rwanda. *International journal of STD & AIDS* 2017; **28**(11): 1082-9.

147. Teclessou JN, Akakpo S, Gbetoglo D, Koumagnanou G, Singo A, Pitche P. HIV prevalence and behavioral studies among female sex workers in Togo in 2015. *Bulletin de la Societe de pathologie exotique (1990)* 2017; **110**(4): 270-5.

148. Hladik W, Baughman AL, Serwadda D, et al. Burden and characteristics of HIV infection among female sex workers in Kampala, Uganda - a respondent-driven sampling survey. *BMC public health* 2017; **17**(1): 565.

149. Eakle R, Bourne A, Mbogua J, Mutanha N, Rees H. Exploring acceptability of oral PrEP prior to implementation among female sex workers in South Africa. *J Int AIDS Soc* 2018; **21**(2).

150. Cowan FM, Davey C, Fearon E, et al. Targeted combination prevention to support female sex workers in Zimbabwe accessing and adhering to antiretrovirals for treatment and prevention of HIV (SAPPH-IRe): a cluster-randomised trial. *Lancet HIV* 2018; **5**(8): e417-e26.

151. Mboup A, Behanzin L, Guedou FA, et al. Early antiretroviral therapy and daily pre-exposure prophylaxis for HIV prevention among female sex workers in Cotonou, Benin: a prospective observational demonstration study. *Journal of the International AIDS Society* 2018; **21**(11): e25208.

152. Kyongo J, Kiragu M, Karuga RN, et al. How long will they take it? Oral pre-exposure prophylaxis (PrEP) retention for female sex workers, men who have sex with men and young women in a demonstration project in Kenya. *22nd International AIDS Conference* 2018.

153. Pillay Y. Challenges of South Africa's sex worker PrEP programme: Lessons learned, moving towards other key populations. *22nd International AIDS Conference* 2018.

154. Lamontagne E, d'Elbee M, Ross MW, Carroll A, Plessis AD, Loures L. A socioecological measurement of homophobia for all countries and its public health impact. *European journal of public health* 2018; **28**(5): 967-72.

155. Beyrer C, Sullivan PS, Sanchez J, et al. A call to action for comprehensive HIV services for men who have sex with men. *Lancet (London, England)* 2012; **380**(9839): 424-38.

156. Hagopian A, Rao D, Katz A, Sanford S, Barnhart S. Anti-homosexual legislation and HIV-related stigma in African nations: what has been the role of PEPFAR? *Global health action* 2017; **10**(1): 1306391.

157. Joint United Nations Programme on HIV/AIDS. Miles to go: closing gaps, breaking barriers, fighting injustices. 2018.

158. Mutua G, Sanders E, Mugo P, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. *PLoS One* 2012; **7**(4): e33103.

159. Van der Elst EM, Mbogua J, Operario D, et al. High acceptability of HIV pre-exposure prophylaxis but challenges in adherence and use: qualitative insights from a phase I trial of intermittent and daily PrEP in at-risk populations in Kenya. *AIDS Behav* 2013; **17**(6): 2162-72.

160. Kimani M, van der Elst EM, Chiro O, et al. PrEP interest and HIV-1 incidence among MSM and transgender women in coastal Kenya. *Journal of the International AIDS Society* 2019; **22**(6): e25323.

161. Karuga RN, Njenga SN, Mulwa R, et al. "How I Wish This Thing Was Initiated 100 Years Ago!" Willingness to Take Daily Oral Pre-Exposure Prophylaxis among Men Who Have Sex with Men in Kenya. *PLOS One* 2016; **11**(4): e0151716.

162. Barnighausen K, Matse S, Hughey AB, Hettema A, Barnighausen TW, McMahon SA. "We know this will be hard at the beginning, but better in the long term": understanding PrEP uptake in the general population in Eswatini. *AIDS care* 2020; **32**(2): 267-73.

163. Clinicaltrials.gov. PrEP Demonstration Study in Swaziland. *Retrieved from https://clinicaltrials-govoffcampuslibwashingtonedu/ct2/show/NCT03254550*

164. Koss C, Ayieko J, Kwarisiima D, et al. PrEP uptake, engagement, and adherence following population-wide HIV testing in rural Kenya and Uganda in the SEARCH study. *International AIDS Conference , 21-24 July* 2019.

165. National AIDS and STI Control Programme. Status on implementation of Oral Pre-exposure Prophylaxis for HIV in Kenya. Nairobi, Kenya, 2018.

166. Jipende JiPrEP. https://twitter.com/NimejiPrEP.

167. Were D, Atkins K, Musau A, Plotkin M, Curran K. Manifestations of stigma in the context of a national oral pre-exposure prophylaxis (PrEP) scale-up program in Kenya. *International AIDS Society, 21-24 July* 2019.

168. Ware NC, Pisarski EE, Haberer JE, et al. Lay Social Resources for Support of Adherence to Antiretroviral Prophylaxis for HIV Prevention Among Serodiscordant Couples in sub-Saharan Africa: A Qualitative Study. *AIDS Behav* 2015; **19**(5): 811-20.

169. Coelho LE, Torres TS, Veloso VG, Landovitz RJ, Grinsztejn B. Pre-exposure prophylaxis 2.0: new drugs and technologies in the pipeline. *Lancet HIV* 2019; **6**(11): e788-e99.

170. Kambutse I, Igiraneza G, Ogbuagu O. Perceptions of HIV transmission and pre-exposure prophylaxis among health care workers and community members in Rwanda. *PLOS One* 2018; **13**(11): e0207650.

171. Pilgrim N, Jani N, Mathur S, et al. Provider perspectives on PrEP for adolescent girls and young women in Tanzania: The role of provider biases and quality of care. *PLoS One* 2018; **13**(4): e0196280.

172. Geibel S, Hossain SM, Pulerwitz J, et al. Stigma Reduction Training Improves Healthcare Provider Attitudes Toward, and Experiences of, Young Marginalized People in Bangladesh. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2017; **60**(2s2): S35-s44.

173. Risher K, Adams D, Sithole B, et al. Sexual stigma and discrimination as barriers to seeking appropriate healthcare among men who have sex with men in Swaziland. *Journal of the International AIDS Society* 2013; **16**(3 Suppl 2): 18715.

174. van der Elst EM, Smith AD, Gichuru E, et al. Men who have sex with men sensitivity training reduces homoprejudice and increases knowledge among Kenyan healthcare providers in coastal Kenya. *J Int AIDS Soc* 2013; **16 Suppl 3**: 18748.

175. van der Elst EM, Gichuru E, Omar A, et al. Experiences of Kenyan healthcare workers providing services to men who have sex with men: qualitative findings from a sensitivity training programme. *Journal of the International AIDS Society* 2013; **16 Suppl 3**: 18741.

176. Pillay Y. South Africa's experience in brining PrEP to scale for a range of populations - SUSA0703. *9th IAS Conference on HIV Science* 2017.

177. Gill K, Dietrich G, Gray G, et al. Pluspills: an open label, safety and feasibility study of oral pre-exposure prophylaxis (PrEP) in 15-19 year old adolescents in two sites in South Africa. *International AIDS Conference; July 23-26* 2017.

178. Irungu E, Ngure K, Mugwanya K, et al. Surmounting PrEP delivery challenges through adaptation of implementation guidelines: Lessons learned from HIV care clinics in Kenya. *IAS 2019* 2019.

179. Wagner L, Roberts S, O'Rourke S, Celum C, Baeten J, Bukusi E. Challenges with oral pre-exposure prophylaxis (PrEP) disclosure among adolescent girls and young women (AGYW) in Kenya and South Africa. *The HIV Research For Prevention Conference (HIVR4P); October 21-25* 2018.

180. Hartmann M, McConnell M, Bekker LG, et al. Motivated Reasoning and HIV Risk? Views on Relationships, Trust, and Risk from Young Women in Cape Town, South Africa, and Implications for Oral PrEP. *AIDS Behav* 2018; **22**(11): 3468-79.

181. Bassett IV, Govere S, Millham L, et al. Contraception, HIV Services, and PrEP in South African Hair Salons: A Qualitative Study of Owner, Stylist, and Client Perspectives. *J Community Health* 2019.

182. Rousseau-Jemwa E, Celum C, Baeten J, Bekker L-G. A comparative study of risk among adolescent girls and young women who accept or decline PrEP uptake from a community-based mobile clinic. *International AIDS Conference; July 23-27* 2018.

183. Tung EL, Thomas A, Eichner A, Shalit P. Implementation of a community pharmacy-based pre-exposure prophylaxis service: a novel model for pre-exposure prophylaxis care. *Sex Health* 2018; **15**(6): 556-61.

184. Ortblad KF, Kearney JE, Mugwanya K, et al. HIV-1 self-testing to improve the efficiency of pre-exposure prophylaxis delivery: a randomized trial in Kenya. *Trials* 2019; **20**(1): 396.

185. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: A systematic review and meta-analysis. *PLOS One* 2018; **13**(9): e0204091.

186. Downing J, Kawuma E. The impact of a modular HIV/AIDS palliative care education programme in rural Uganda. *Int J Palliat Nurs* 2008; **14**(11): 560-8.

187. Todd CS, Mills SJ, Innes AL. Electronic health, telemedicine, and new paradigms for training and care. *Curr Opin HIV AIDS* 2017; **12**(5): 475-87.

188. Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. *The Lancet Infectious diseases* 2014; **14**(11): 1055-64.

189. Murnane PM, Heffron R, Ronald A, et al. Pre-exposure prophylaxis for HIV-1 prevention does not diminish the pregnancy prevention effectiveness of hormonal contraception. *AIDS (London, England)* 2014; **28**(12): 1825-30.

190. Mugwanya KK, Baeten JM, Wyatt C, et al. Brief Report: Frequency of Monitoring Kidney Function in HIV-Uninfected Persons Using Daily Oral Tenofovir Disoproxil Fumarate Pre-

exposure Prophylaxis. *Journal of acquired immune deficiency syndromes (1999)* 2018; **77**(2): 206-11.

191. Heffron R, Mugo N, Hong T, et al. Pregnancy outcomes and infant growth among babies with in-utero exposure to tenofovir-based preexposure prophylaxis for HIV prevention. *AIDS (London, England)* 2018; **32**(12): 1707-13.

192. van der Straten A, Stadler J, Montgomery E, et al. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. *PLOS One* 2014; **9**(2): e89118.

193. Ongwen P, Musau A, Were D, Mutegi J, Wakhutu B, Reed J. Adolescent girls on PrEP: Findings from Kenya's oral PrEP scale-up supported by Jilinde. *International AIDS Society* 2019.

194. World Health Organization. Health Systems in Africa: Community Perceptions and Perspectives. The Report of a Multi-Country Study. Brazzaville, Republic of Congo: World Health Organization: Regional Office for Africa, 2012.

195. Babalola TK, Moodley I. Assessing the Efficiency of Health-care Facilities in Sub-Saharan Africa: A Systematic Review. *Health Serv Res Manag Epidemiol* 2020; **7**: 2333392820919604.

196. Azevedo MJ. The State of Health System(s) in Africa: Challenges and Opportunities. *Historical Perspectives on the State of Health and Health Systems in Africa, Volume II* 2017: 1-73.

197. Curran K, Baeten JM, Coates TJ, Kurth A, Mugo NR, Celum C. HIV-1 prevention for HIV-1 serodiscordant couples. *Curr HIV/AIDS Rep* 2012; **9**(2): 160-70.

198. Baeten JM, Heffron R. Pre-exposure prophylaxis to intensify the fight against HIV. *Lancet Infect Dis* 2014; **14**(6): 443-5.

199. Pawson M, Grov C. 'It's just an excuse to slut around': gay and bisexual mens' constructions of HIV pre-exposure prophylaxis (PrEP) as a social problem. *Sociol Health Illn* 2018; **40**(8): 1391-403.

200. Nakasone SE, Chimbindi N, Mthiyane N, et al. "They have this not care - don't care attitude:" A Mixed Methods Study Evaluating Community Readiness for Oral PrEP in Adolescent Girls and Young Women in a Rural Area of South Africa. *AIDS Res Ther* 2020; **17**(1): 55.

201. Greener R, Milford C, Bajunirwe F, et al. Healthcare providers' understanding of HIV serodiscordance in South Africa and Uganda: implications for HIV prevention in sub-Saharan Africa. *Afr J AIDS Res* 2018; **17**(2): 137-44.

202. Mashaphu S, Burns JK. Couples-based interventions in the context of HIV discordance. *S Afr J Psychiatr* 2017; **23**: 1009.

203. Matthews LT, Crankshaw T, Giddy J, et al. Reproductive counseling by clinic healthcare workers in Durban, South Africa: perspectives from HIV-infected men and women reporting serodiscordant partners. *Infect Dis Obstet Gynecol* 2012; **2012**: 146348.

204. Kimemia G, Ngure K, Baeten JM, et al. Perceptions of pregnancy occurring among HIV-serodiscordant couples in Kenya. *Reprod Health* 2019; **16**(1): 85.

205. Ngure K, Kimemia G, Dew K, et al. Delivering safer conception services to HIV serodiscordant couples in Kenya: perspectives from healthcare providers and HIV serodiscordant couples. *J Int AIDS Soc* 2017; **20**(Suppl 1): 21309.

206. Heaton LM, Bouey PD, Fu J, et al. Estimating the impact of the US President's Emergency Plan for AIDS Relief on HIV treatment and prevention programmes in Africa. *Sex Transm Infect* 2015; **91**(8): 615-20.

207. Irungu E, Ngure K, Mugwanya K, et al. Surmounting PrEP delivery challenges through adaptation of implementation guidelines: Lessons learned from HIV care clinics in Kenya. 10th International AIDS Society Conference on HIV Science. Mexico City; 2019.

208. National AIDS Control Council. Kenya HIV Prevention Revolution Road Map: Count Down to 2030. Nairobi, Kenya: Ministry of Health, Kenya, 2014.

209. Kyongo JK, Kiragu M, Karuga R, et al. How long will they take it? Oral pre-exposure prophylaxis (PrEP) retention for female sex workers, men who have sex with men and young women in a demonstration project in Kenya. *22nd International AIDS Conference* *http://programmeaids2018org/Abstract/Abstract/8788* 2018.

210. Hennink M, Stephenson R. Using research to inform health policy: barriers and strategies in developing countries. *J Health Commun* 2005; **10**(2): 163-80.

211. Moral standards for research in developing countries: from "reasonable availability" to "fair benefits". *Hastings Cent Rep* 2004; **34**(3): 17-27.

212. Ongolly FK, Dolla A, Ngure K, et al. "I just decided to stop: " Understanding PrEP discontinuation among individuals initiating PrEP in HIV care centers in Kenya. *J Acquir Immune Defic Syndr* 2021.

213. Ngure K, Ongolly F, Dolla A, et al. "I just believe there is a risk" understanding of undetectable equals untransmissible (U = U) among health providers and HIV-negative partners in serodiscordant relationships in Kenya. *J Int AIDS Soc* 2020; **23**(3): e25466.

214. Irungu EM, Ngure K, Mugwanya KK, et al. "Now that PrEP is reducing the risk of transmission of HIV, why then do you still insist that we use condoms?" the condom quandary among PrEP users and health care providers in Kenya. *AIDS Care* 2020: 1-9.

215. Irungu E, Mugwanya K, Bukusi E, et al. High PrEP use in African men and women continuing PrEP in public health HIV clinics Conference of Retroviruses and Opportunistic Infections (CROI); 2019; Seattle, Washington; 2019.

216. Pintye J, Kinuthia J, Roberts DA, et al. Brief Report: Integration of PrEP Services Into Routine Antenatal and Postnatal Care: Experiences From an Implementation Program in Western Kenya. *J Acquir Immune Defic Syndr* 2018; **79**(5): 590-5.

217. Sila J, Larsen AM, Kinuthia J, et al. High Awareness, Yet Low Uptake, of Pre-Exposure Prophylaxis Among Adolescent Girls and Young Women Within Family Planning Clinics in Kenya. *AIDS Patient Care STDS* 2020; **34**(8): 336-43.

218. Were D, Musau A, Mutegi J, et al. Using a HIV prevention cascade for identifying missed opportunities in PrEP delivery in Kenya: results from a programmatic surveillance study. *J Int AIDS Soc* 2020; **23 Suppl 3**(Suppl 3): e25537.

219. ClinicalTrials.gov. The Prevention Options for Women Evaluation Research (POWER) Cohort; ClinicalTrials.gov Identifier: NCT03490058 (https://www.clinicaltrials.gov/ct2/show/NCT03490058).

220. Siegler AJ, Mayer KH, Liu AY, et al. Developing and Assessing the Feasibility of a Home-based Preexposure Prophylaxis Monitoring and Support Program. *Clin Infect Dis* 2019; **68**(3): 501-4.

221. Ortblad KF, Mogere P, Roche S, et al. Design of a care pathway for pharmacy-based PrEP delivery in Kenya: results from a collaborative stakeholder consultation. *BMC Health Serv Res* 2020; **20**(1): 1034.

222. ClinicalTrials.gov. PrEP My Way: A Novel PrEP Delivery System to Meet the Needs of Young African Women; ClinicalTrials.gov Identifier: NCT04408729 (https://clinicaltrials.gov/ct2/show/NCT04408729).

223. Havlir DV, Balzer LB, Charlebois ED, et al. HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa. *N Engl J Med* 2019; **381**(3): 219-29.

224. Hayes RJ, Donnell D, Floyd S, et al. Effect of Universal Testing and Treatment on HIV Incidence - HPTN 071 (PopART). *N Engl J Med* 2019; **381**(3): 207-18.

225. Iwuji CC, Orne-Gliemann J, Larmarange J, et al. Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial. *Lancet HIV* 2018; **5**(3): e116-e25.

226. Makhema J, Wirth KE, Pretorius Holme M, et al. Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana. *N Engl J Med* 2019; **381**(3): 230-42.

227. Havlir D, Lockman S, Ayles H, et al. What do the Universal Test and Treat trials tell us about the path to HIV epidemic control? *J Int AIDS Soc* 2020; **23**(2): e25455.

228. Grulich AE, Guy R, Amin J, et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. *Lancet HIV* 2018; **5**(11): e629-e37.

229. Buchbinder SP, Havlir DV. Getting to Zero San Francisco: A Collective Impact Approach. *J Acquir Immune Defic Syndr* 2019; **82 Suppl 3**(Suppl 3): S176-s82.

230. Aarons GA, Sklar M, Mustanski B, Benbow N, Brown CH. "Scaling-out" evidence-based interventions to new populations or new health care delivery systems. *Implement Sci* 2017; **12**(1): 111.