PROTOCOL

HIV self-testing and PrEP to increase testing and prevention uptake among male partners and improve postpartum ART use in PMTCT B+ programs in Uganda

PrEP as a bridge to PMTCT Study

Version 2.0

16 August 2017

Funding:

United States National Institute of Mental Health

(R01 MH113434)

TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS **3**

STUDY TEAM **4**

SUMMARY **5**

Specific Aims *6*

BACKGROUND & RATIONALE **8**

STUDY METHODS **12**

Overall design *12*
Objectives *13*
Population *15*
Eligibility *15*
Sample size *15*
Recruitment *15*
Study screening *16*
Study enrollment *17*
Study procedures *17*
Counseling about PrEP and ART *21*
PrEP medication and dispensation *22*
PrEP adherence *22*
PrEP safety *22*
Retention *23*
HIV testing *23*
HIV seroconversion *24*
Final study visit *24*
Quantitative surveys *25*
Data quality and management *25*
Qualitative data collection *25*
Qualitative data quality and management *27*
Qualitative data analysis *27*

DATA ANALYSIS **28**

Sample size *28*
Outcome measurements *28*
Statistical considerations *29*

DATA SHARING AND OWNERSHIP **29**

DISSEMINATION PLAN **30**

HUMAN SUBJECTS CONSIDERATIONS **30**

Informed consent *30*
Risks *31*
Benefits *32*
Treatment for injury *33*
Study records *33*
Confidentiality *34*

REFERENCES **38**

ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal Care
ART	Antiretroviral Therapy
CHCT	Couple HIV Counseling and Testing
CRF	Case Report Form
FTC/TDF	Co-formulated Emtricitabine-Tenofovir Disoproxil Fumarate
HIV	Human Immunodeficiency Virus
HIVST	HIV Self-testing
HTS	HIV Testing Services
IDI	In-depth Interview
IRB	Institutional Review Board
IPV	Intimate Partner Violence
KCCA	Kampala Capital City Authority
MU-JHU	Makerere University – Johns Hopkins University Research Collaboration
OR	Odds Ratio
PMTCT	Prevention of Mother-To-Child HIV Transmission
PrEP	Pre-Exposure Prophylaxis
RA	Research Assistant
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SOC	Standard of Care
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

STUDY TEAM

Infectious Disease Institute, Kampala, Uganda

Elly Katabira, MBChB, FRCP
Andrew Mujugira, MBChB, PhD
Nulu Bulya, MBChB, MSc
Timothy Muwonge, MBChB, MPH

Makerere University-Johns Hopkins PMTCT research collaboration

Zikulah Namukwaya, MBChB, MPH

University of Washington, Seattle, USA

Connie Celum, MD, MPH
Jared Baeten, MD, PhD
Deborah Donnell, PhD
Renee Heffron, PhD, MPH

Harvard University, Boston, USA

Norma Ware, PhD
Monique Wyatt, PhD

University of North Carolina-Chapel Hill

Harsha Thirumurthy, PhD

SUMMARY

Uganda has the fifth highest HIV burden globally and one of the highest fertility rates in Africa. Prevention of mother-to-child HIV transmission Option B+ (PMTCT B+) is national policy in Uganda. To maximize the prevention and clinical benefits of PMTCT B+, the challenges of low HIV testing by male partners and high rates of post-partum discontinuation of antiretroviral therapy (ART), insufficient adherence, and incomplete viral suppression need to be addressed. Women may be more likely to continue ART long-term and have higher adherence post-partum if their partner is tested, there is mutual disclosure of HIV status, and their partner takes ART or PrEP, depending on his status. Innovative approaches are needed to allow men to test in settings other than busy antenatal clinics, preferably where they have privacy, are comfortable and do not miss work. Innovative HIV testing technology – HIV self-testing (HIVST) could increase male partner engagement in HIV testing, and uptake of prevention and care services through linkage to highly effective pre-exposure prophylaxis (PrEP) and ART for all HIV-positive men. This study has been designed to address this gap through an enhanced PMTCT B+ program with HIV self-testing, and linkage to PrEP or ART, for male partners.

In a demonstration project we recently completed among mutually disclosed East African HIV serodiscordant couples (the Partners Demonstration Project), integrated ART and PrEP delivery with time-limited PrEP for the HIV-negative partner as a 'bridge' until the HIV-positive partner was on ART for six months, and achieved viral suppression, was very acceptable, achieved very high uptake and adherence to ART and PrEP, and nearly eliminated HIV transmission. This protocol builds on that demonstration project by evaluating whether PMTCT outcomes are improved by increasing uptake of HIV testing and PrEP among HIV-negative men whose pregnant partner is HIV-positive. PrEP for HIV-negative male partners of HIV-positive pregnant women provides highly effective prevention benefits during an important 'season of risk' when men may have higher HIV acquisition risk from their partner if she is viremic (during the first few months after ART initiation, post-partum ART discontinuation or due to viral resistance), or from outside partners.

We will conduct a randomized trial to evaluate whether provision of oral HIV self-test kits to HIV-positive pregnant women overcomes male partners' reluctance to be tested in PMTCT clinics. Pregnant women will be trained in the use and interpretation of HIVST, and given two oral fluid-based HIVST kits to use with or give to their partners, along with information about HIV testing and prevention and care services. We will offer men confirmatory testing regardless of their HIV test result through HIVST, counseling, and if negative, PrEP and if positive, ART. We will provide counseling to minimize social harms of HIV self-testing, and additional counseling and referral to social support services when social harms occur. This project will address key challenges in PMTCT B+ programs, by evaluating innovative strategies to increase male partner involvement coupled with offering PrEP to HIV-negative men, ART to HIV-positive men, and encouraging post-partum ART continuation and adherence among HIV-positive women.

Design:	Randomized clinical trial Up to 12 months of post-partum follow-up
Population:	HIV-positive pregnant women in Kampala, Uganda who have a male partner of unknown HIV status (approximately 500 women in total)
Study Sites:	Kasangati Couples Center and collaborating antenatal care (ANC) clinics in Kampala, Uganda

Approach: We will recruit HIV-positive women ≥18 years accessing PMTCT B+ programs in Kampala, who have a male partner of unknown HIV status. Women will be randomized to the intervention (HIVST) or the control arm (invitation letters to deliver to partners to come to the ANC clinic where she receives care or Kasangati Couples Center for HIV testing). Women will be instructed in the use and interpretation of HIVST and be provided two HIVST kits to give to or use with their male partners. We will recommend that HIV-negative men use PrEP until their partner has been on ART for at least 6 months, and that HIV-positive men take ART. **Specifically, PrEP as a bridge to ART will be offered to HIV-negative male partners as follows: when the HIV-positive pregnant partner is not yet taking ART, PrEP will be offered, and when the HIV-positive pregnant partner initiates ART, PrEP will be provided for the HIV-negative male partner for six months (i.e., when viral suppression in the HIV-positive partner would be expected to be typically achieved).** This bridge to ART approach is detailed in Figure 1.

Specific Aims

Aim 1: Determine whether an enhanced PMTCT program with HIV self-testing for male partners and provision of PrEP to HIV-negative male partners increases the proportion of male partners who test for HIV and men who initiate PrEP.

Innovations are needed to reach male partners for HIV testing that allow men to test where they are comfortable, which typically is not in busy antenatal clinics. Provision of HIV self-tests (HIVST) to pregnant women for their partners is safe, acceptable, and effective, and could facilitate partner testing, and increase uptake of PrEP by HIV-negative men and ART by HIV-positive men. HIVST is a promising approach to increasing partner and couples testing, which has not yet been evaluated in the context of PMTCT B+ programs. We will randomize 500 HIV-positive women initiating PMTCT B+ in Kampala in a 2:1 ratio to one of two partner testing strategies: 1) HIVST kits (intervention) to give to or use with their partner, or 2) invitation letters for fast-track testing at the clinic (standard of care). Men who test will be offered confirmatory testing and counseling. Men who test HIV-positive will be linked to ART, and men who test HIV-negative will be offered PrEP for the first six months after his partner initiates ART through PMTCT.

The co-primary outcomes are the proportion of male partners who test for HIV and the proportion of HIV-negative male partners who initiate PrEP.

Aim 2: Evaluate whether HIV testing combined with PrEP and ART use among male partners increases effective post-partum ART use among HIV-infected Ugandan women in PMTCT B+.

Pregnant HIV-positive women may be more likely to continue ART after delivery and have higher adherence post-partum if their partners are tested, there is mutual disclosure of HIV status, and their partner takes ART or PrEP, depending on his status. We will evaluate ART use and viral suppression at 12 months post-partum among the 500 HIV-positive pregnant women who are randomized to male partner

testing strategies (Aim 1). In this observational analysis, we will use causal inference methods to assess whether the outcome (women's viral load at 12 months post-partum) is improved by the exposure (male partner testing and engagement in HIV care or prevention – PrEP use among HIV-negative men and ART use among HIV-positive men).

The primary outcome is viral suppression at 12 months, as a measure of the woman's effective ART use in the first 12 months post-partum and her adherence. Viral suppression will be defined as plasma viral load <400 copies/ml at 12 months post-partum. We will analyze the outcome (viral suppression in the female) by the male partner's testing outcome and PrEP use among HIV-negative men. Secondary outcomes include a) post-partum adherence, as measured by pharmacy records, which will be used to measure ART dispensation, and women's self-report about treatment interruptions; b) infant HIV status at 6 weeks as determined by PCR results (HIV infected/uninfected); and c) infant survival at 12 months as reported by the mother.

Aim 3: Assess the acceptability of HIV self-testing and PrEP to pregnant women taking part in PMTCT B+ and to their male partners, using qualitative and quantitative methods.

PMTCT B+ has the secondary benefit of reducing HIV transmission to male partners if HIV-positive women continue antiretroviral therapy (ART) long-term with high adherence. However, optimizing the effectiveness of PMTCT requires understanding factors that influence low uptake of HIV testing by male partners (~1/5 of partners of women in Uganda PMTCT programs are tested for HIV). In addition, previous studies have indicated that 1/3-1/2 of African women discontinue ART after delivery, and the importance of disclosure and partners' engagement in HIV care or prevention need to be assessed to determine how much those factors influence ART continuation post-partum.

We will use quantitative and qualitative methods to investigate acceptability of HIVST and PrEP. Quantitative behavioral data will be collected from the study cohort during clinic visits using multiple validated questionnaires. A structured interview administered to all HIV-infected female partners at enrollment will ask about knowledge of the partner's HIV status, disclosure, fertility desires, relationship power, and intimate partner violence. Up to 100 individual interviews will be conducted. A purposefully selected subsample of up to 90 individuals will take part in qualitative in-depth interviews to achieve in-depth understanding of the acceptability of HIV self-testing and PrEP use by male partners to women in PMTCT B+ and to male partners. In a sample of 10 PMTCT providers, we will assess perspectives of HIVST, facilitated disclosure, male partner linkage to HIV care and prevention, and women's ART use post-partum.

The goal of the qualitative analysis is to assess the acceptability of HIV self-testing and PrEP use by pregnant women in PMTCT B+, their male partners, and implementation perspectives of PMTCT providers.

BACKGROUND & RATIONALE

The past five years have increased the pace of progress towards controlling the HIV epidemic and reducing the number of new perinatal and sexually transmitted infections occurring each year. The major reason is effective treatment and prevention through antiretrovirals – used by HIV-positive individuals to treat HIV infection (ART) and prophylactically by HIV-negative individuals to prevent HIV infection (PrEP). However, much work remains to optimize ART and PrEP delivery to millions of people with and at high risk of HIV using strategies that will achieve the greatest effectiveness and coverage possible [3]. Uganda carries the fifth highest HIV burden in the world, with 1.6 million people living with HIV, and 140,000 new infections and 63,000 AIDS-related deaths in 2013 [4]. Uganda also has a high fertility rate (5.8 pregnancies per woman in 2015). A key driver of HIV incidence in Uganda is low utilization of antenatal and delivery services [5]. HIV-positive women are more likely to complete the PMTCT cascade when male partners are tested and engaged in care [6]. To have a greater impact of PMTCT B+ on HIV trends in Uganda in the context of a high fertility rate, it is critical to increase male HIV testing and uptake of PrEP or ART and women's post-partum ART continuation.

PMTCT B+ and the need for higher rates of ART use and adherence post-partum

Although there has been substantial progress in implementation of PMTCT B+, several challenges remain and need to be addressed, including post-partum ART continuation and adherence. These gaps and needs are highlighted by recent analyses from the PROMISE study, which was conducted in 52 clinical research sites in eight countries. The PROMISE study showed low acceptance of early ART among postpartum women globally (PROMISE studies 1077 BF/FF/HS). Women in PROMISE were informed of the benefits of early ART from the landmark START trial [7], but 33% did not accept early ART, citing concerns of i) wanting more time to consider ART and ii) stating she feels well [8]. Thus, despite intense ART education and HIV monitoring in a well-resourced clinical trial setting, one-third of women required additional counseling to start ART earlier for their own health.

The PROMISE study also included a randomized comparison of stopping or continuing ART in 1653 postpartum non-breastfeeding women with pre-ART CD4≥400 cells/mm^3 (PROMISE study 1077HS). This study demonstrated clinical benefits of post-partum ART; women who were randomized to continue ART had a 32% lower risk of reaching the primary endpoint of time to an AIDS event, and a 44% lower risk of reaching an AIDS event or a WHO stage 2 or 3 event [9]. Importantly, among women randomized to continue ART, 23% had virologic failure; 86% of women with viremia did not have genotypic resistance, indicating non-adherence as the likely cause of their viremia [9]. Interventions to improve adherence are needed to achieve long-term benefits in post-partum women on ART.

In contrast, in our recently completed demonstration project of integrated PrEP and ART delivery with 1013 high-risk HIV serodiscordant couples in Kenya and Uganda, the rate of viral suppression at 12 months was higher in women who initiated ART during pregnancy than for other indications (96% vs 87%, p=0.02) [10]. This finding merits further study for integrated PrEP and ART delivery in PMTCT B+ programs to improve effective ART use post-partum, when coupled with safe, acceptable, and effective strategies to increase HIV testing in male partners of unknown status, and to motivate male partners who test to use of PrEP or ART, based on their serostatus and with effective linkage strategies.

Low uptake of HIV testing by male partners: A barrier to PMTCT B+ success

HIV testing is consistently lower among African men than women, leading to a higher proportion of undiagnosed HIV infection among men [11, 12]. Women who learn they are HIV-positive, often in antenatal care, are sometimes unwilling to disclose their HIV status due to fear of domestic violence, stigmatization or divorce [13]. Safe and acceptable solutions to this challenge need to be identified in order to optimize the benefits of PMTCT for mothers and infants; past research has shown that HIV-positive women are more likely to complete the PMTCT cascade when their male partners are tested and engaged in care [6]. Male partner involvement increases condom use [14, 15], women's utilization of antenatal services and HIV testing [16-18], obtaining HIV results [19], ART use [14, 19, 20], adherence to infant feeding advice [21-24], infant HIV testing [25], and infant HIV-free survival [25, 26]. Despite these multiple benefits, studies from Africa have found that male partner testing rates remain low (16-54%) [14, 20, 27, 28]. Barriers to male partner involvement include fear of knowing one's status, stigma [28, 29], men's belief that their status is the same as their partners (i.e., testing by 'proxy') [23], cultural norms that men should not accompany their wives to antenatal care [13], negative attitudes of health care workers [30, 31] (i.e., not allowing men in antenatal clinics) [29, 30, 32], and men's concern about time away from work and the impact on their income [29, 31-34].

Health system facilitators of male engagement in PMTCT

Multiple interventions have tried to increase male involvement in PMTCT programs, including the provision of personalized invitation letters to men whose female partners have engaged with the program. Men often perceive invitation letters as a medical prescription, which increases their sense of obligation to attend [13]. However, partner return following receipt of official invitation letters is not high –36% in Kenya [35], 26-35% in South Africa [36], 28% in Malawi [37] and 16% in Uganda [38]. Couples HIV testing and counseling improves uptake of HIV testing and ART without increased risk of social harm, compared with individual counseling [14, 39]. Other approaches include offering ANC services for couples during weekends or non-working hours [13] and intra-partum HIV testing and counseling [40]. Couples testing, flexible hours, expedited clinic processing for women who bring male partners [40], male support groups [31] and peer sensitization of men [29] modestly increased male partner involvement in some PMTCT programs, but have not achieved substantially large increases in partner testing.

Self-testing kits as innovation in HIV testing of male partners of pregnant HIV-positive women

HIVST is a highly acceptable and innovative approach to increasing knowledge of HIV serostatus among many populations that have limited access to or low uptake of HIV testing services [41-43]. Studies conducted in high- and low-income settings have shown that self-tests can be used accurately by lay users [44], and that they overcome various barriers to facility-based testing [41, 45]. Self-tests offer a low-cost way to increase access to testing among hard to reach persons such as male partners of pregnant women. This potential was demonstrated by our colleague, Dr. Thirumurthy, in a pilot of HIVST which offered multiple self-tests to HIV-negative women in antenatal and postpartum care in Kisumu, Kenya. Women were shown how to correctly use oral fluid-based self-tests, given three test kits with written and pictorial instructions, to distribute or use the tests with their male partner, based entirely on their discretion. Notably, over 90% of women distributed HIVST kits to their partners, and reported safer sexual decisions and rare social harms [46]. Acceptability indicators were very high; women reported HIVST kits were easy to use and their partners welcomed the opportunity to learn their HIV status conveniently and privately. To further evaluate this approach, Dr. Thirumurthy conducted a RCT of distribution of HIVST by pregnant and postpartum women to promote male partner and couples testing through antenatal clinics in Kisumu, Kenya [47]. Women in the intervention group received 2 oral fluid-based HIVST, while those in the comparison group were given referral vouchers that invited their

partner for HIV testing at clinics, alone or as a couple. The primary outcome was whether their partner had sought HIV testing in the past 3 months. Significantly higher rates of male partner testing were achieved in the HIVST arm (91% compared to 51% in the control arm), and couples testing increased by 42% and disclosure by 39% [47].

In the context of PMTCT B+ programs, HIVST is a promising approach to increasing male partner and couples testing, which has not yet been evaluated. The Kenyan pilot of secondary distribution of HIVST to male partners of pregnant women had encouraging results; however, only a minority (4%) of the 600 women enrolled were HIV-positive and thus more information is needed about how to tailor this approach to HIV-infected women in PMTCT programs. Specific aspects that need to be better understood are HIV-positive pregnant women's willingness and ability to motivate their male partner to test, which may differ from HIV-negative pregnant women, as well as social harms which may be more likely when male partners learn that their partner is HIV-positive. The importance of evaluating HIVST for male partners of women in PMTCT is that their male partners will either be HIV-negative (and thus in an HIV serodiscordant partnership where they could benefit from PrEP or voluntary medical male circumcision) or HIV-positive and need linkage to HIV care and ART. In summary, the feasibility and impact of secondary distribution of HIVST need to be evaluated in PMTCT B+ programs with the expectation that HIV-positive women will require additional counseling and support to broach HIVST with their partners.

PMTCT B+ in Uganda

Since PMTCT B+ became Ugandan national policy in late 2012, 94% of HIV positive pregnant women receive ART to reduce risk of mother-to-child transmission. Retention of women 6 months after ART initiation during pregnancy was 88% [48], and 90% on ART had undetectable viral load after >6 months of ART. While progress is being made in ART uptake among pregnant women in PMTCT B+ programs in Uganda, male engagement remains low (23%) [5]. Mulago Hospital is the main referral hospital in Uganda, where ~23,000 pregnant women attended antenatal clinics in 2015, 85% received an HIV test, and 3.3% were HIV positive with an average of 54 women initiating ART per month in PMTCT B+. Male partner involvement strategies at Mulago include invitation letters and phone calls to encourage HIV testing and assist with disclosure. Their experience with these strategies is mixed, as many invitation letters were not delivered. However, when letters were delivered, men showed up, eager to find out why the doctor wanted to see them. Partners who came to clinic were given priority and seen quickly, to boost retention, since the main complaint of men is the time to attend clinic. In the Mulago PMTCT program, however, only 19% of male partners were tested. Retention in care 12 months after ART initiation was only 60% in 2015.

Offering HIVST to women and facilitating men's access to services are potential innovations to improve male partner testing and PMTCT outcomes. In Uganda, HIVST is currently limited to research studies. The Ugandan Ministry of Health (MoH) and Minister of Science, Technology and Innovation have expressed interest in HIVST projects, including this project which could improve PMTCT B+ outcomes.

Antiretrovirals to reduce HIV infectiousness and acquisition

The source of up to half of all new HIV infections in Africa is estimated to be among HIV serodiscordant couples – in which one partner is HIV-positive and the other is HIV-negative – a priority target population for HIV prevention interventions [49, 50]. Based on our experience in testing thousands of couples in East and southern Africa in past research studies, approximately half of male partners of HIV-positive women are expected to test HIV-negative and be in an HIV

serodiscordant partnership and half to test HIV-positive [51].

Following diagnosis of HIV serodiscordancy, couples face challenges as they strive to preserve their relationship and keep the HIV-negative partner uninfected amidst desires for intimate sex and safe pregnancy [52, 53], PrEP for the HIV-negative partner and ART for the HIV-positive partner can provide high levels of protection and a long-term solution for HIV serodiscordant couples [54, 55].

ART use by HIV-positive persons, with high adherence and maintenance of viral suppression, is the ultimate goal for long-term prevention of HIV transmission within HIV serodiscordant couples [7, 56]. The time between ART initiation and viral suppression (up to 6 months) [57], and common delays in ART initiation [58] are the period of highest HIV risk for HIV-negative partners. During this period PrEP can provides near complete protection to an HIV-negative person – the basis of an integrated PrEP and ART strategy [59]. Multiple randomized trials among different at-risk populations have demonstrated high efficacy of tenofovir-based PrEP [60-63].

The 2015 WHO guidelines recommend PrEP for people with substantial HIV risk, operationalized as populations with ≥3% annual HIV incidence, including HIV serodiscordant couples [64]. With release of WHO guidelines, there is growing enthusiasm for PrEP implementation in resource-limited settings; Kenyan and South African drug authorities rapidly approved PrEP in 2015 [64, 65]. Implementation plans have been developed in Kenya, South Africa, and are being developed in Uganda and other African countries. The focus for PrEP implementation is on innovative approaches to PrEP delivery for high-risk populations, such as HIV-negative male partners of women in PMTCT B+ programs. These implementation strategies require evaluating men's willingness to be tested through innovative methods, their PrEP uptake, and women's post-partum ART use and adherence.

PrEP as an effective bridge to ART and viral suppression

We tested the effectiveness of an integrated PrEP and ART strategy in our recently-completed Partners Demonstration Project among 1,013 ARV-naïve HIV serodiscordant couples at 4 sites in Uganda and Kenya, including the Kasangati Couples Center in Kampala (NIMH R01 MH095507, Bill & Melinda Gates Foundation OPP1056051, USAID AID-OAA-A-12-00023) [59]. In this model, PrEP provides protection against HIV acquisition prior to viral suppression in the HIV-positive partner (Figure 1, Scenario 1). For couples in which the positive partner does not initiate ART immediately upon diagnosis, the period of HIV risk is extended and PrEP is used for a longer period of time (Figure 1, Scenario 2). We recruited couples with a predicted HIV incidence of ≥3% [66], who would most benefit from PrEP as a bridge to ART.

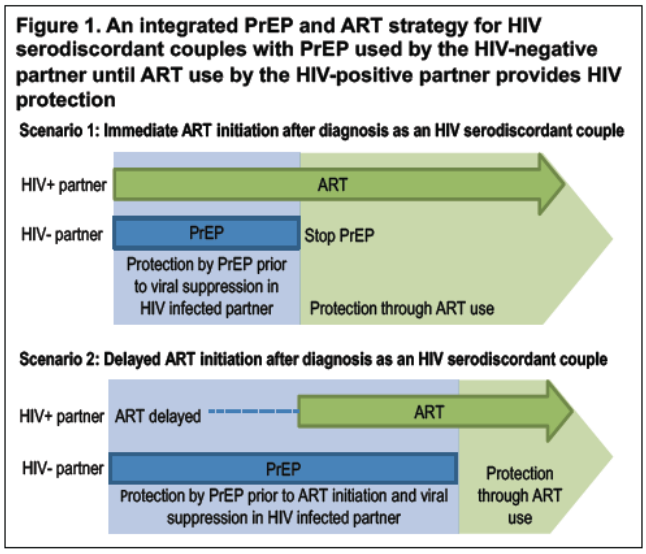
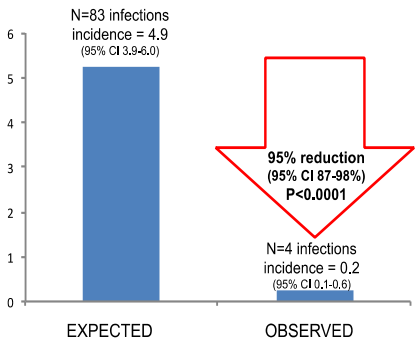


Figure 1. An integrated PrEP and ART strategy for HIV serodiscordant couples with PrEP used by the HIV-negative partner until ART use by the HIV-positive partner provides HIV protection

Overall, 97% of HIV-negative partners in the Partners Demonstration Project initiated PrEP and had high adherence with tenofovir detected in 82% of plasma samples. Similarly, we observed

Figure 2. Observed vs expected HIV infections in the Partners Demonstration Project, with near elimination of HIV transmission[1, 2].



high uptake and adherence to ART among HIV-infected partners; 91% initiated ART by 24 months with >90% viral suppression [59]. The integrated PrEP and ART strategy accelerates ART initiation; 90% of HIV-positive partners initiated ART within six months, compared to 50% in the Partners PrEP Study [58]. This integrated PrEP and ART strategy nearly eliminated HIV transmission with 95% reduction in HIV transmission (Figure 2); observed infections were compared to a counterfactual simulation model, bootstrapping data from the placebo arm of Partners PrEP, and sampling for the subset with a matching distribution of risk scores and follow-up [59]. High protection was observed among HIV-negative men (95% HIV reduction, p<0.0001), relevant to this project [67]. We found PrEP until the HIV-positive partner initiated ART was highly acceptable, safe and effective [1, 2]. Thus, the Partners Demonstration Project provided strong evidence of high adherence and effectiveness of time-limited PrEP among HIV serodiscordant couples who were counseled about their risk of HIV exposure, who were young and many wanted children, and were counseled about the efficacy of PrEP and ART. These findings provided critical data for PrEP guidelines by WHO [64, 68], Kenya [65], and Ugandan guidelines, which are in development.

Relevant to this project, we also evaluated the feasibility and acceptability of HIVST among HIV-negative persons on PrEP in a sub study of the Partners Demonstration Project. Specifically we evaluated HIVST in Thika, Kenya, in which HIV-negative partners on PrEP were provided two oral HIVST kits to use monthly between their quarterly visits. We found very high acceptability, with 99% of users reporting that HIVST kits were easy to use, empowering, and reduced anxiety between quarterly clinic-based HIV testing [69].

Summary

This project will address key challenges in PMTCT B+ programs, by evaluating innovative strategies to increase male partner testing through secondary distribution of HIVST by the female partners to overcome men's reluctance to test involvement in PMTCT. Confirmatory testing needs to follow with HIVST, and in the context of testing male partners of women in PMTCT B+, men who test will either learn that they are HIV negative and thus in an HIV serodiscordant partnership or HIV-positive. Thus, the linkages to HIV prevention and care are critical, and we will couple HIV testing with offering PrEP to HIV-negative men and ART to HIV-positive men, and encouraging post-partum ART continuation and adherence among HIV-positive women.

STUDY METHODS

Overall design

This is a randomized trial of HIV-positive pregnant women and their partners. The overall goal is to evaluate the impact of innovative strategies on male partner HIV testing, and engagement in HIV care and prevention among men, on post-partum ART continuation and adherence among HIV-positive women. We will recruit HIV-positive women in PMTCT B+ programs in Kampala to be randomized to: 1) the intervention arm in which they receive HIVST kits for their partners with

self-instruction materials about HIVST, encouragement to seek confirmatory testing and counseling along with a voucher and referral, and brief educational materials about PrEP and ART, or 2) the control arm in which they receive invitation letters to deliver to their partners that invite men to fast-track HIV testing at the clinic, along with brief educational materials about PrEP and ART. Women in the intervention arm will be instructed in the use and interpretation of HIVST and be provided two HIVST kits to give to or use with their male partners. Male partners will receive an educational brochure outlining the benefits of HIV testing and ART or PrEP. We will recommend that HIV-negative men use PrEP until their partner has been on ART for at least 6 months post-partum, and that HIV-positive men take ART.

The co-primary outcomes of the study are the proportion of male partners who test and the proportion of HIV-negative male partners who take PrEP. The primary analysis is an intent to treat comparison by randomization arm of the primary outcome: proportion of women whose male partners who test HIV-uninfected and initiate PrEP within six months after their HIV-positive partner is randomized. A secondary outcome is an objective marker of PrEP adherence - tenofovir detection at 3 and 6 months - among men who initiate PrEP.

The secondary outcome is the proportion of HIV-infected women who are virally suppressed at 12 months post-partum, as the measure of continuation of ART and high adherence post-partum. We will also conduct observational analyses using marginal structural models to assess whether the HIV-positive woman's viral load at 12 months post-partum is improved by male partner testing and engagement in HIV care or prevention (PrEP use among HIV-negative men or ART use among HIV-positive men). Quantitative and qualitative methods will be used to assess acceptability of HIVST in PMTCT, PrEP among male partners who test negative, and identify ways to minimize social harms.

Objectives

Aim 1: **Determine whether an enhanced PMTCT program with HIV self-testing for male partners and provision of PrEP to HIV-negative male partners increases the proportion of male partners who test for HIV and men who initiate PrEP.**

Innovations are needed to reach male partners for HIV testing that allow men to test where they are comfortable, which typically is not in busy antenatal clinics. Provision of HIV self-tests (HIVST) to pregnant women for their partners is safe, acceptable, and effective, and could facilitate partner testing, and increase uptake of PrEP by HIV-negative men and ART by HIV-positive men. HIVST is a promising approach to increasing partner and couples testing, which has not yet been evaluated in the context of PMTCT B+ programs. We will randomize 500 HIV-positive women initiating PMTCT B+ in Kampala in a 2:1 ratio to one of two partner testing strategies: 1) HIVST kits (intervention) to give to or use with their partner, or 2) invitation letters for fast-track testing at the clinic (standard of care). Men who test will be offered confirmatory testing and counseling. Men who test HIV-positive will be linked to ART, and men who test HIV-negative will be offered PrEP for the first six months after his partner initiates ART through PMTCT.

The co-primary outcomes are the proportion of male partners who test for HIV and the proportion of HIV-negative men who initiate PrEP. The secondary outcome for this Aim is tenofovir detection at 3 and 6 months among men who use PrEP.

Aim 2: Evaluate whether HIV testing combined with PrEP and ART use among male partners increases effective post-partum ART use among HIV-infected Ugandan women in PMTCT B+.

Pregnant HIV-positive women may be more likely to continue ART after delivery and have higher adherence post-partum if their partners are tested, there is mutual disclosure of HIV status, and their partner takes ART or PrEP, depending on his status. We will evaluate ART use and viral suppression at 12 months post-partum among the 500 HIV-positive pregnant women who are randomized to male partner testing strategies (Aim 1). In this observational analysis, we will use causal inference methods to assess whether the outcome (women's viral load at 12 months post-partum) is improved by the exposure (male partner testing and engagement in HIV care or prevention – PrEP use among HIV-negative men and ART use among HIV-positive men).

The primary outcome is viral suppression at 12 months, as a measure of the woman's effective ART use in the first 12 months post-partum and her adherence. Viral suppression will be defined as plasma viral load <400 copies/ml) at 12 months post-partum. Secondary outcomes include: a) post-partum adherence, as measured by pharmacy records will be used to measure ART dispensation and women's self-report about treatment interruptions; b) infant HIV status at 6 weeks as determined by PCR results (HIV-infected/uninfected); and c) infant survival at 12 months as reported by the mother.

Aim 3: Assess the acceptability of HIV self-testing and PrEP for pregnant women taking part in PMTCT B+ and their male partners, using qualitative and quantitative methods.

PMTCT B+ has the secondary benefit of reducing HIV transmission to male partners if HIV-positive women continue antiretroviral therapy (ART) long-term with high adherence. However, optimizing the effectiveness of PMTCT requires understanding factors that influence low uptake of HIV testing by male partners (~1/5 of partners of women in Uganda PMTCT programs are tested for HIV In addition, previous studies have indicated that 1/3-1/2 of African women discontinue ART after delivery, and the importance of disclosure and partners' engagement in HIV care or prevention need to be assessed to determine how much those factors influence ART continuation post-partum.

We will use quantitative and qualitative methods to investigate acceptability of HIVST and PrEP. Quantitative behavioral data will be collected from the study cohort during clinic visits using multiple validated questionnaires. A structured interview administered to all HIV-infected female partners at enrollment will ask about knowledge of the partner's HIV status, disclosure, fertility desires, relationship power, and intimate partner violence. Up to 100 individual interviews will be conducted. A purposefully selected subsample of up to 90 individuals will take part in qualitative in-depth interviews to achieve in-depth understanding of the acceptability of HIV self-testing and PrEP use by male partners to women in PMTCT B+ and to male partners. In a sample of 10 PMTCT providers, we will assess perspectives about HIVST, facilitated disclosure, male partner linkage to HIV care, and women's ART use post-partum.

The goal of the qualitative analysis is to assess the acceptability of HIV self-testing and PrEP use by pregnant women in PMTCT B+, their male partners, and implementation perspectives of PMTCT providers.

Population

Five hundred HIV-positive pregnant women, ≥18 years of age, with male partners of unknown status, will be recruited from PMTCT B+ programs in Kampala. Women in the intervention arm will receive HIVST kits to give to or use with their partner. Women in the standard of care arm will receive invitation letters that invite the male partner to be tested at the clinic where their pregnant partner receives antenatal care, or at the Kasangati Couples Center.

Eligibility

For all participants

- Able and willing to provide written informed consent
- Able and willing to provide adequate locator information for study retention purposes

For women

- Age ≥18
- Currently pregnant
- HIV-positive based on positive rapid HIV tests, according to national algorithm
- Not currently enrolled in an HIV treatment study
- Male partner not known to be HIV-positive or has not tested in the past 3 months

For men

- In partnership with an HIV-positive pregnant woman in PMTCT B+

Sample size

A total of 500 HIV-positive pregnant women and their male partners.

Recruitment

The Kasangati Couples Center has long-established recruitment and retention strategies to identify and enroll research-naive participants for prospective follow up. Recruitment materials will be approved by the IRB before study initiation. Recruitment materials will educate women about the benefits of male partner testing, the probability of being HIV serodiscordant, and risks of post-partum ART discontinuation for the woman's health and the possibility of HIV transmission to her baby and partner.

Women attending antenatal care are offered HIV testing, and those who test positive are provided immediate ART according to Uganda national HIV treatment and prevention guidelines. Approximately, 50 HIV-positive women are identified per month. The Couples Center will work directly with collaborating health facilities, including MU-JHU and Kasangati antenatal care/PMTCT programs, to identify pregnant HIV-positive women attending PMTCT B+. Health care workers and study staff at collaborating clinics will provide general information sessions to inform potential participants.

Study screening

Women will be enrolled and followed at collaborating ANC clinics. Trained research staff will counsel potentially eligible women about the benefits of male partner testing, post-partum ART persistence, and possible participation in the study. Counseling messages will include:

Reasons for male partners to be tested for HIV:

- To know his status.
- So that if he is infected that they don't infect others.
- If he is positive, to help him to access care and treatment which will help him stay healthy longer.
- If he is negative, to help him stay HIV negative.
- To strengthen their relationship.
- To avoid testing by proxy since about half the time, he will have a different status than his partner.

HIV status disclosure:

- Does your partner know your status?
- If no, and you are positive, what do you think might happen if you discuss this with your partner?
- Where would you tell him? When would you tell him?
- Encourage women to tell him a story about the antenatal clinic, how other women have encouraged their partners to test for HIV, which has been beneficial for the family by keeping both partners health longer, and see what kind of reaction he has.
- Importance of talking about HIV together with their partner so they can plan for the future.
- Risk of HIV for their children.
- Explore the possibilities of being sent away, relationship ending, violence, etc.

Intimate partner violence:
The counselor will collect the following information in a culturally appropriate way.

- In the past month, has your current partner punched, slapped, kicked, bit you, or caused you any type of physical harm?
- In the past month, has your current partner insulted, ignored or humiliated you, yelled at you, or made you feel ashamed or bad about yourself?
- In the past month, has your current partner forced you to have sex or perform any sexual act, or touched you sexually in any way that you did not want?
- In the past month, has your current partner made you feel afraid, unsafe or in danger?
- In the past month, has your current partner taken your money when you didn't want him to, or prevented you from working outside the home?

Women who indicate a willingness to participate will provide independent informed consent for study screening. Male partners who self-test for HIV and come to clinic for confirmatory testing or come for HIV testing in response to an invitation letter will be offered the opportunity to consent for screening. Men will consent to participate in the stud and receive open label PrEP or ART, depending on HV status. Participants will be asked screening questions about their medical history, including specific questions about prior pregnancies, any medical problems, partner's status, HIV testing, and whether they think violence would result from offering a HIVST kit to their partner.

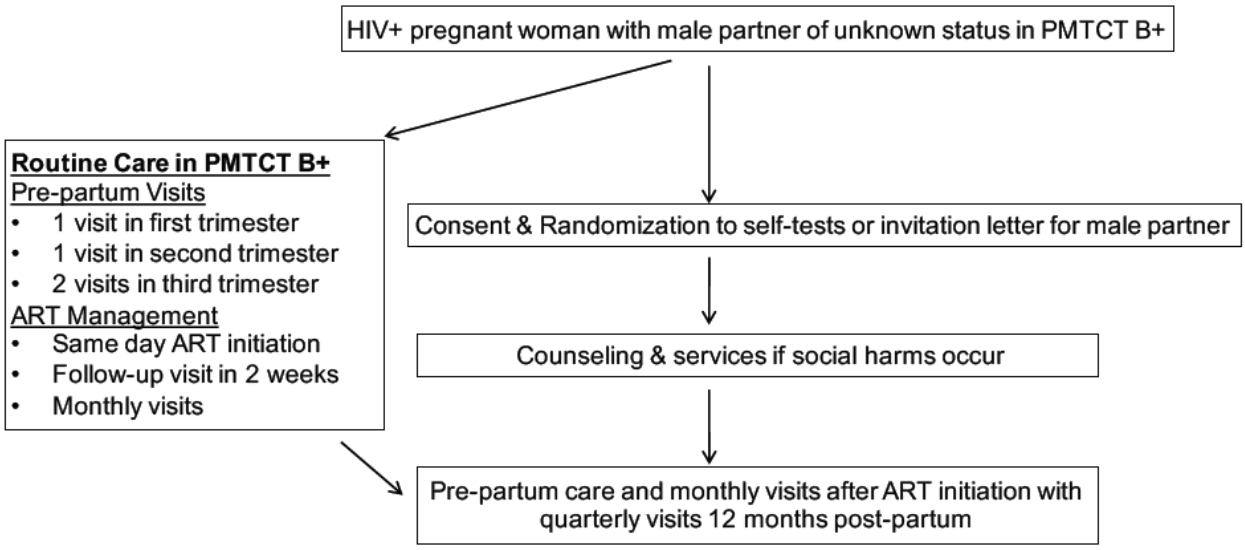
Study enrollment

Each participant will be asked to provide independent informed consent for study participation. Women who meet eligibility criteria, and are willing to participate in the study for 12 months post-partum, will be consented and enrolled. Trained clinicians will perform physical exams, including measurement of blood pressure, height, and weight.

Study procedures

Specific study procedures are depicted in Figure 3 and detailed in Tables 5-7.

Figure 3: Study Procedures for HIV+ Pregnant Women in PMTCT B+



Female partner randomization

HIV-positive pregnant women will be randomized in a 2:1 ratio to provision of HIVST kits to use with their male partners or to take an invitation letter to their male partner to be tested at their ANC clinic, or if the male prefers, the Kasangati Couples Center. The 2:1 randomization provides more data on male partner testing with HIVST, which would be useful in assessing uptake, social harms, and linkage to PrEP and ART. There is ample historical information about male partner testing with invitation letters; the objective of this protocol is to maximize the learning about implementation and outcomes with secondary distribution of HIVST through PMTCT B+.

The randomization code and resulting randomization list will be generated and maintained by the study statistician or designee. A variable size block randomization scheme will be implemented to produce the randomization list and maintained by the study biostatistician. Thus, neither participants nor study staff will be blinded to each participant's randomization group assignment.

HIVST intervention group

Pregnant women will be provided a brief demonstration of how to use the self-test, and will be given two oral fluid based HIV self-tests (Oraquick rapid HIV-1/2 test kit with developer fluid vial and stand) to take home with written and pictorial instructions translated into Luganda (the local language) about HIVST to share with their partner. The instructions will clearly indicate how to

perform an oral swab, how long to wait to read results, and how to interpret the results. Women will receive information about HIV self-testing including reasons for suggesting usage of the self-test to their partner, and strategies for introducing self-tests to their partners; however, it will also be emphasized that women are under no obligation to suggest to their partner or convince him to use the self-test. Because use of self-tests at home will mean that a trained counselor will not be present when women or their partners take the test, the counselor will discuss with women what messages might best suit her situation, so that she and her partner can use the self-tests correctly and safely on their own. A counselor will be available by phone if a woman in the self-test arm needs help explaining counselling messages to their partner. The messages and counseling that we will provide will adhere to Uganda National Guidelines for HIV Testing Services [70].

Counseling messages:

- Knowing your partner's status will help you make better decisions to protect your partner and unborn children from HIV.

- This HIV self-test kit is an HIV test that you can use at home. We will show you how to use it, and you can take it home today to use yourself and to give to your partner to use.

- We are giving you 2 HIV self-test kits and encourage you to give one to your partner, and use the second one for yourself, so that you test together.

- We will ask if you have any questions or concerns about how you might want to talk to your partner about using the HIV self-test. If you think he may react violently, you should not bring up the topic with him or wait for an opportune time to do so.

- This is how you could introduce the self-test kits to your husband/partner:

    a) Place the test kit where he is most likely to see it. When he inquires about it, say you went to the clinic and was taught about the new self-test-kit … and it is a good opportunity to test together.

    b) Gauge his mood, and if it is good, ask him about the last time he was tested/you tested as a couple, then tell him you were given HIV self-tests at the clinic and it is a good opportunity to test together.

    c) Ask him whether he has heard about the new HIV test kit which uses saliva … then you could tell him that you were given some kits and it would be a good opportunity to test together and know each other's HIV status.

- If your partner agrees to self-test either with you or alone, remember that the test result is preliminary and should be confirmed at the clinic.

- After you or your partner uses the self-test kit, you can keep the used test kit(s) until you return the used test kit to the clinic.

- You are not required to use the test kits, it is a choice. It is also not mandatory to bring the used test kit back.

Counselors will provide tailored messaging about HIV concordant positive or serodiscordant

results, additional counseling as needed, encourage joint prevention decision making, and facilitate linkage to HIV prevention, treatment and care services.

Each HIVST kit will include positively framed messages, informational materials, and a voucher with unique identifying numbers for men who use the self-test to come to a clinic for confirmatory testing. Test kits will also clearly indicate a 24-hour "helpline" to call in case questions arise about how to use the tests, obtain support in case of a reactive test, where to go for confirmatory testing, or where to seek additional counseling; this helpline will also be useful for providing additional support and referrals to women who may experience social harms.

In addition, we will provide a brief educational sheet about the importance of their HIV testing as a first step; if they are HIV-positive they can stay healthy by taking ART and if they are HIV-negative, they can remain HIV negative and healthy by taking PrEP. Both will help be beneficial for them and their family.

Returned test strips will be used to verify use and not HIV test results.

Minimizing probability of violence associated with participants' offering HIV testing to sexual partners:
To minimize the likelihood of social harms, including violence against HIV-positive pregnant women participants, trained study staff will talk to participants at the time of enrollment about the importance of *using their discretion* and *assessing the risk of intimate partner violence (IPV)* when deciding whether to introduce self-testing to their partners. Study staff will also talk to participants about strategies for introducing self-testing or voluntary counseling and testing (VCT) referral voucher to partners, including talking points. It will be emphasized to study participants that they are not obligated to distribute self-tests to their partners. Participants will be counseled to never offer a self-test or invitation letter to a partner who they will believe will become violent due to introducing HIV testing.

Having developed the training materials for study staff and implemented the intervention successfully in the Kenya pilot study, we are confident that these procedures help minimize the risks of social harms and intimate partner violence. We will also provide study participants with information on where they can seek help if they do experience violence or do need advice. We will establish a support telephone line (hotline) that study participants or their sexual partners can call at any time that will put them in touch with the study coordinator. The study coordinator will help arrange support for any woman experiencing violence. In our pilot study we set up a hotline similar to what is proposed here.

Minimizing probability of adverse reactions to test results and ensuring receipt of appropriate services: To ensure correct usage of self-tests (in the intervention group) and to minimize the probability of psychological distress due to HIV testing, we will include simple instruction materials with each self-test on how to use the tests, in English and Luganda. The self-test will include information listing VCT clinics in the area where free HIV testing and counseling is available, including the ANC clinic where his partner receives care and the Kasangati Couples Center. Information will also be provided on clinics in the area where free HIV care and treatment is available. A support telephone line (hotline) will allow study participants or their sexual partner to call at any time in order to be in touch with study staff, who will be ready to provide additional information on where to seek further testing, care or treatment.

Partner invitation group

Women in the control arm will be provided invitation letters, the standard of care, to deliver to their partner to come for HIV testing to their ANC clinic for fast-track testing or at Kasangati Couples Center, alone or as a couple. As in the intervention group, each invitation letter will include positively framed messages to men about the opportunity to receive PrEP and ART if they get tested. Letters will also include information on how to contact a 24-hour "helpline" to talk with a counselor about the meaning of results and referrals. Invitation letters will have unique numbers to allow linkage of the man's testing to his partner. Letters will be collected at the Kasangati Couples Center, the MU-JHU PMTCT program, and collaborating ANC clinics.

Antenatal and postnatal care

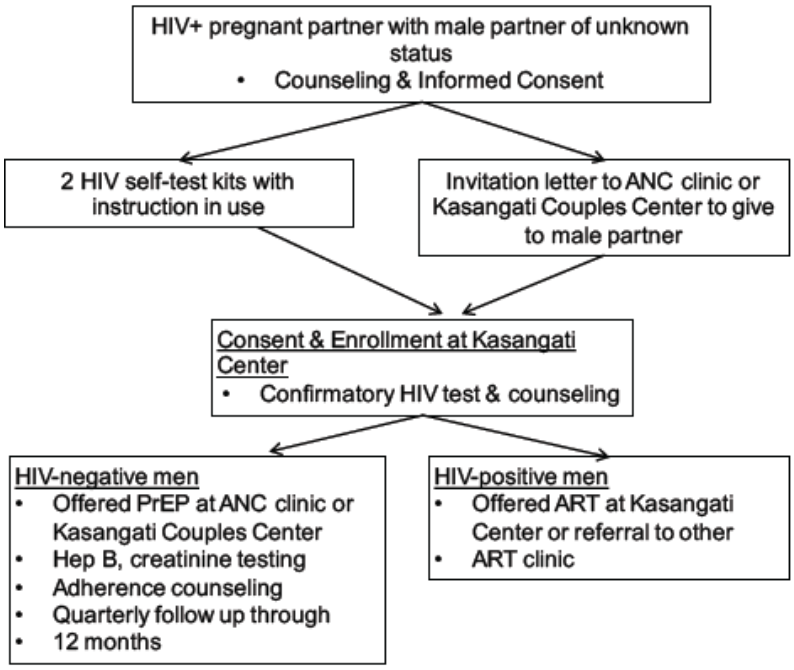
Data collection will occur during standard of care antenatal/postnatal visits. HIV-positive pregnant women will access routine care at antenatal clinics according to guidelines for preventing and treating HIV infection in Uganda [71]. Pregnant women will have up to 4 antenatal visits before delivery: 1 visit in the first trimester, 1 visit in the second trimester and 2 visits in the third trimester. The standard-of-care antenatal package includes cotrimoxazole preventive therapy, nutrition assessment, iron, folic acid and multivitamin supplementation and screening for syphilis. Women newly initiating ART in PMTCT B+ will have same-day pre-ART adherence counselling and ART initiation (Table 1). They will have PMTCT B+ follow-up visit two weeks after initiating ART, and monthly visits for ART refills thereafter until delivery. Women will be offered delivery at a facility of their choice. After delivery, women will be followed quarterly for up to 12 months.

Brief study questionnaires will be administered will occur at the PMTCT visits to avoid separate study-specific visits. Postnatal care and infant immunization visits will follow the routine maternal and child health (MCH) schedule. Viral load (VL) monitoring will include plasma HIV RNA levels at enrollment, 6 and 12 months post-partum. Blood samples will be batch-tested at the MU-JHU Virology lab. Women will be asked about interruptions in ART use. If the mother is stable on ART with good adherence and undetectable VL, post-partum visits will be quarterly thereafter. During clinic visits, women will complete interviewer-administered surveys to collect data on behavioral factors that could mediate women's post-partum use of ART. Women will be provided their viral load results at the next visit with counseling about the relationship between adherence, viral load and transmission risk.

Male partner procedures

Male partners of women enrolled in the study will be recruited using established recruitment methods for serodiscordant couples. These strategies operationalize protocol-specified requirements and ensure participant privacy for eligibility determination. Men will be referred to their partner's antenatal clinic or the Kasangati Couples Center, either through invitation letters for HIV testing or following HIVST for confirmatory testing (Figure 4). Men will undergo informed consent for HIV testing and referral for HIV care and ART if they test HIV-positive, or offered PrEP if they test HIV-negative. Trained research staff will counsel potentially eligible men about possible participation in the study. Men who indicate a willingness to participate in the study for up to 12 months post-partum will be offered an opportunity to undergo study screening.

Figure 4: Study Procedures for Male Partners



Counseling about PrEP and ART

Participants will receive behavioral counseling on the effectiveness of ART and 6 months of PrEP to bridge to ART for HIV serodiscordant couples, post-partum ART continuation and adherence, PrEP benefits and adherence for HIV-negative male partners, and clinical and prevention benefits of ART for HIV-positive men. Counseling sessions will occur every 3 months, either to each partner individually or as a couple. Ad hoc sessions will be provided when requested by couples (Figure 5). Counselors will stress the importance of post-partum ART persistence with high adherence for clinical benefits and to prevent onward HIV transmission to breastfeeding infants and sexual partners.

Table 1. Components of HIV prevention delivery for HIV serodiscordant couples as standard of care public health clinics & enhanced PMTCT B+ with integrated ART and PrEP

SOC services for HIV serodiscordant couples	Additional components of integrated PrEP with PMTCT B+
Behavioral counseling	Couples: counseling on HIV serodiscordance & efficacy of integrated PrEP and ART for (enrollment)
Condom provision	HIV-positive women: counseling on post-partum ART continuation & adherence for women (antenatal visits, delivery, 3, 6, 9 and 12 months)
PrEP counseling & provision	HIV-negative men: counseling about PrEP benefits & adherence (enrollment, quarterly visits through up to 12 months)
6-monthly CD4 testing	HIV-negative men: assessment of acute HIV infection, PrEP provision
Annual HIV RNA testing, plus suspected virologic failure	HIV-positive women: HIV RNA testing (enrollment, 6 & 12 months) HIV negative men: 6-monthly renal function monitoring, blood archive for tenofovir testing (3 & 6 months) HIV-positive men: assessment of ART use

Counselors will assess men's willingness to initiate PrEP or ART, willingness of women to continue ART post-partum, strategies to maintain daily adherence to PrEP and ART, the time-

limited use of PrEP, other HIV risk reduction strategies (condom use, medical male circumcision, and treatment of sexually transmitted infections), and couples communication. Male partners will be supported to make informed choices. Acute HIV symptoms will be assessed before PrEP dispensation. Medication refills with 3-month supplies, ART and PrEP adherence counseling, condoms, HIV testing, and lab monitoring (6-monthly creatinine, CD4 and HIV RNA testing) will be provided (Table 1).

PrEP medication and dispensation

PrEP will be offered to HIV-negative men according to national guidelines [71], and with the recommendation to take it for 6 months after their partner starts ART or until she is virally suppressed. Male partners will be assessed for acute HIV infection, counseled on PrEP and offered PrEP, if it is desired and there are no acute HIV symptoms. PrEP will be dispensed in a 3-monthly supply. HIV testing will be conducted at each quarterly visit prior to providing PrEP refills. PrEP use will be suspended if HIV tests are positive or if acute HIV infection is suspected. Renal monitoring will occur on a 6-monthly basis.

The study will provide open-label PrEP to HIV-negative male partners for 6 months or until their HIV-infected female partner is virally suppressed. Co-formulated FTC/TDF at 200 mg / 300 mg respectively will be used. The dose of FTC/TDF is the standard dose approved by the U.S. Food and Drug Administration. The study drug will be stored in accordance with the drug manufacturer's recommendations. The pharmacy and storage facility will have locked, climate-controlled environments, with controlled humidity and temperature to remain within limits allowed by the manufacturer for drug storage. Counseling on the medications being used, their side effect profiles, how to take the study medication, what to do if side effects are experienced, and the importance of not sharing study medication to optimize potential efficacy will be provided.

PrEP adherence

High adherence is important for PrEP effectiveness in preventing HIV acquisition. Study staff also will provide brief adherence counseling at each scheduled visit, to mimic "real world" counseling. Data on adherence to the product use regimen will be collected via standardized interviewer-administered questions to ascertain product use. PrEP use will be measured by dispensing records, and self-report through a validated 3-item questionnaire. Clinic and pharmacy records will be used to document PrEP prescriptions at the ANC clinics and Kasangati Couples Center, abstracted in real time from pharmacy records and entered into an electronic database. Adherence will also be assessed through tenofovir drug levels in male partners 3 and 6 months after PrEP initiation.

PrEP safety

The Partners PrEP Study demonstrated that PrEP (including FTC/TDF) was safe for use in heterosexual men and women in Uganda. There were no statistically significant differences in the frequency of deaths, serious adverse events, adverse events overall, or key laboratory adverse events for those receiving PrEP compared to those receiving placebo [72].

For the purposes of this study, only serious adverse events (SAEs) and adverse events Grade 3 and above related to PrEP use will be obtained. All AEs that result in a clinical hold or permanent discontinuation of PrEP will be reported on the AE Log CRF regardless of grade.

With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to SAEs will be obtained and required data elements will be recorded on study CRFs. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Reporting on adverse events to relevant IRBs will be according to relevant regulations.

Retention

Retention measures for pregnant women and male partners will be those regularly used in previous PrEP studies at the Kasangati Couples Center – reminder calls, text messages, peer support, and home visits when individuals have several missed visits or an abnormal test result. Couples who break up will remain in the study but have separate clinic visits. We will continue to collect data about sexual behavior and PrEP and ART use. Research procedures for men will include behavioral questionnaires and blood collection to test for tenofovir drug concentration levels among men using PrEP.

HIV testing

HIV testing will be performed in accordance with Uganda HIV testing algorithms [73]. Men who are tested through HIVST will receive a voucher for confirmatory testing, either at the ANC where their partner receives care or at Kasangati Couples Center. HIV testing for men in the invitation letter arm and confirmatory testing for men in the HIVST arm will be accompanied by post-test counseling. All counseling and testing approaches will be in accordance with Uganda HIV counseling and testing guidelines.

Procedures for HIV-positive men

Men who are HIV-positive will receive ART adherence support, clinical monitoring and quarterly refills. A baseline CD4 count will be used to screen for risk of opportunistic infections. Treatment will be provided by local HIV care providers or at the Kasangati Couples Center. The recommended first line regimen in Uganda is tenofovir-lamuvidine-efavirenz. Newly initiated partners shall be seen monthly for the first 3 months and quarterly therafter according to national guidelines. At these visits, adherence to ART, drug intolerance, side effects/toxicities and response to ART will be assessed. Viral load monitoring will occur at the 6 month visit (standard of care). Viral load results will be used to support adherence counseling.

Follow up study procedures

All data collection will be conducted in a private room in the participant's preferred language, according to the participant's fluency and preference. Women in the intervention and control groups will be asked about their partner's testing and outcome at their PMTCT visits. Women in the intervention arm will be asked to bring the used HIV test strip to the ANC clinic or Kasangati Couples Center, where confirmatory testing will be offered. Clinic-based confirmatory testing for partners will confirm the accuracy of self-test results and identify false-positive results. Women

whose partners have not tested will be encouraged to come with their partners to the ANC clinic or the Kasangati Couples Center to receive counseling about the importance of HIV testing, PrEP for men who are in HIV serodiscordant partnerships, ART for HIV-positive men, and intimate partner violence, efficacy of ART and PrEP, and her adherence for ART to reduce the risk of maternal-child transmission and sexual transmission. Women in the intervention and control groups whose partners do not come to Kasangati, will be asked whether they discussed HIV testing with their partner, whether their partner was tested elsewhere, the outcome of his test, and whether any social harms resulted.

At each follow up visit, questionnaires will be administered to assess sexual behavior, self-perceived risk, partner testing status, intimate partner violence, relationship power, future fertility desires, self-efficacy, stigma, facilitators and barriers to ART and PrEP (Table 2).

Table 2. Data collection to longitudinally assess behavioral factors related to PrEP and ART use among HIV serodiscordant couples in PMTCT B+

Behavioral data	Assessment tool
HIV-positive women	
Facilitators and barriers to ART use and adherence in women (Aim 2)	Tool piloted in Partners Demonstration Project and past qualitative and quantitative work [59, 74]
Sexual behavior with study partner and other partners	Tool piloted in multiple couples-based HIV prevention services [59, 75]
Internalized stigma	Internalized AIDS-related stigma scale [76]
Fertility desires	Tool piloted in multiple couples-based HIV prevention services [59, 75]
Relationship power	Sexual Relationship Power Scale [77]
Intimate partner violence	Conflict Tactics Scale [78, 79]
Alcohol use	Rapid Alcohol Screen [78]
Self-efficacy of ART use	HIV Medication Self-Efficacy Scale [80]
HIV-negative men	
HIV prevention preferences among men (Aim 1)	Tool piloted in multiple couples-based HV prevention studies [59, 75]
Self-perceived risk of HIV	Tool piloted in multiple couples-based HIV prevention services [59, 75]
Sexual behavior with study partner and other partners	Tool piloted in multiple couples-based HIV prevention services [59, 75]
HIV-positive men	
Sexual behavior with study partner and other partners	Tool piloted in multiple couples-based HIV prevention services [59, 75]

HIV seroconversion

Study staff will counsel male partners who seroconvert on PrEP and refer them to local HIV care providers for ongoing-care and initiation of antiretroviral therapy according to Uganda treatment guidelines. Seroconverters will be asked to remain in the study until completion of the follow up period in order to implement data collection relevant to secondary outcomes -- antiretroviral resistance, plasma viral load and CD4 after HIV seroconversion.

Final study visit

Women and male partners will be followed for 12 months post-partum. At 12 months post-partum

or when a participant discontinues study participation, they will have a final study visit. Study procedures at this visit will be similar to other follow up visits. All study participants on ART will continue receiving care at a public health clinic of their choice. Participants on PrEP will be referred for care if PrEP becomes available through the public health system.

Quantitative surveys

A structured interview administered to all HIV-infected female partners at enrollment will ask about knowledge of the partner's HIV status, disclosure, fertility desires, relationship power, and intimate partner violence. At the enrollment visit for male partners, a structured questionnaire will be administered addressing HIV testing history and experience with HIV testing through the PMTCT program. At six months following enrollment, a structured questionnaire will be administered to women and men about acceptability of HIVST and social harms and benefits associated with HIVST and PrEP for male partners.

Data quality and management

Health information about the mother and child during pregnancy, delivery and after delivery will be documented in the Ministry of Health Mother Child Health Passport. Clinic and pharmacy records will be used to document PrEP prescriptions at the Kasangati Couples Center, abstracted in real time from pharmacy records to tablet-based case report forms and entered into an electronic database. Automated legal range checks will be programmed to reduce data entry errors and internal quality control reports will be run monthly. Our team has experience using this data capture method in other studies of HIV prevention.

Qualitative data collection

Qualitative data collection will consist of individual in-depth interviews (IDIs) and field observations.

IDIs
The qualitative sample of study participants will be stratified by study arm. Specifically, we will carry out 1) up to 45 interviews with male partners (half who receive self-testing kits; half who receive letters of invitation); 2) up to 45 interviews with pregnant women (half whose partners receive self-testing kits; 25 whose partners receive letters of invitation), and 3) PMTCT and HIV providers (up to 10).

Individual in-depth interviews will be conducted with individuals in the qualitative subsample to elicit data on acceptability of HIV self-testing and PrEP for male partners (and on the control condition). Interviews will be "minimally structured", i.e. guided by topics (rather than pre-designated, open-ended questions) tailored to each group. Examples of topics for interviews with male partners are:

a) History of HIV testing;
b) History of relationship with his partner in PMTCT B+;
c) Response to receiving an HIVST or letter of invitation to test;

d) Response to the offer of PrEP for prevention (for individuals with negative test results).

Examples of topics to be covered in the interviews with women in PMTCT B+ are:

1) The "story" of providing the HIV self-testing kit or the letter of invitation to test to their partner
2) Description of the partner's response
3) Partner follow-up in terms of confirmatory HIV testing and/or PrEP
4) Impact on the relationship (including social harms)
5) Impact on feelings about ART use post-partum

Examples of topics to be covered in the interviews with PMTCT providers are:

1) Perceptions of influences on male partner testing in the context of PMTCT B+ ;
2) Experiences of implementing male partner testing in the context of PMTCT B+;
3) Perceived responses of male partners to self-testing, and the reasons behind these responses;
4) Perceived responses to the offer of PrEP for male partners who test negative;
5) Patterns of and influences on ART adherence for pregnant women during pregnancy and post-partum;
6) Perceived impact of HIV testing and subsequent initiation of PrEP or ART by male partners on ART adherence for pregnant and post-partum women; and
7) Perspectives on how to facilitate disclosure and minimize social harms in these couples.

Interview procedures: In-depth interviews will be conducted by gender-matched Ugandan research assistants (RA). The RA's have been trained in methods of qualitative interviewing by Dr. Wyatt, who heads the qualitative team with Dr. Ware. Interviews will be scheduled 1–3 months following provision of the HIVST kit or letter of invitation to test. They will be conducted where conversations cannot be overheard. Interviews will be conducted in the interviewee's language of preference (English or Luganda). Provider interviews will be conducted in English. Interviews will be audio-recorded with permission. Participation will be recognized with a small reimbursement, based on local standards. Compensation for travel to the interview will be provided where appropriate.

Producing the interview data: The interview data for this study will consist of 100 written transcripts. Immediately following each interview session, the interviewer will produce an exact electronic write-up of the interview in English, using audio-recording and notes taken during the interview as guides. We have developed this approach of direct transcription into English from local languages over many years of qualitative research in Africa and find it produces an accurate transcript while also saving time and resources. We will use Express Scribe, an audio-recording transcription computer software program, which facilitates transcription.

Field Observations

This study will use field observations to provide additional, complementary information on implementation of the HIV self-testing intervention (and control condition). Field observations are a well-established data collection technique in qualitative research that involve the presence of a researcher in a naturalistic setting, the witnessing of events and activities of interest, and often some degree of participation [81]. Observations provide a direct view of the event under study and thus complement the mediated perspective obtained through IDIs. Dr. Ware has been using field observations with success in her qualitative HIV research in sub-Saharan Africa for the past several years. The qualitative component of this study will include 20 observations of interactions between pregnant women and providers in PMTCT B+ clinic visits where HIV self-testing kits or letters of invitation to test are distributed. Field observations will be conducted at the Couples

Center by a Ugandan qualitative RA, trained and experienced in this approach to qualitative data collection. Observations will be conducted until 20 observations have been completed. Each observation session will last 2-3 hours. To minimize bias in collecting observational data, dates of observations will be randomly selected. Verbal consent is obtained to conduct observations, which is done by the Ugandan RA. Observations are recorded as field notes, which do not contain identifying information and serve as formal records for analysis.

Qualitative data quality and management

Data in the form of interview transcripts and field notes will be continuously reviewed for content, clarity, detail, and grammar by Dr. Ware's research group. Feedback on quality and suggestions for improvement will be provided to the RA through regular supervision. Upon completion, transcripts and field notes will be routed electronically to Boston, using a secure file transfer system. Data will be stored on secure servers at the Harvard Medical School and at the Kasangati office.

Qualitative data analysis

The goal of the qualitative analysis is to assess the acceptability of HIV self-testing and PrEP for male partners to pregnant women in PMTCT B+ and to male partners. The construct of acceptability is broadly defined to target not only participants' feelings and attitudes toward the intervention, but also their broader experiences with intervention components. The qualitative analysis will address "how" and "why" questions about intervention dynamics to inform future dissemination and intervention examples of questions to be answered through analysis of the qualitative data are:

1) When participating male partners completed an HIV test, what were the reasons?
2) When participating male partners did not test, what were the reasons?
3) In what ways, if any, did the availability of HIV self-testing kits influence the decision to test?
4) In what ways, if any, did receiving a letter of invitation influence men's decision to test?
5) In what ways, if any, did self-testing or letters of invitation impact men's decisions for or against initiation of PrEP and/or ART, for male partners who tested for HIV?

We will use an inductive, content analytic approach [82] to data analysis, with coding and category construction as core analytic activities. The qualitative data set consists of up to 100 interview transcripts and 20 observation field notes. Analysis will begin with open-coding through review of 20% of the data to identify sections of text suggestive of acceptability. These sections of text will be labeled, defined, and illustrated to become codes**,** and assembled into a codebook**.** The codebook will be used for data coding, using the software program Atlas.ti to organize the coding process. Coding will be conducted by the Uganda RA and Emily Pisarski. Data will be sorted by codes to identify themes corresponding to specific aspects of acceptability. The coded data will also be compared by code across groups to investigate systematic inter-group differences in perspectives of male partners, pregnant women and providers. Differences will be reported in descriptive categories. The final step in analysis is to develop descriptive categories. Categories will consist of a label, an operational definition and text specifying the category content, with illustrations through excerpts from interview transcripts or field notes. The categories will represent answers to the analytic questions specified above. Qualitative results will be compared with quantitative data on intervention acceptability collected as part of Aim 3. Qualitative data will be used to help interpret the results of the randomized trial.

DATA ANALYSIS

Sample size

Aim 1: The sample size was selected to ensure high power for the PrEP outcome as well as the male partner testing. Table 3 shows a range of assumptions for the proportion of men who are HIV-uninfected (60-70%), and the test uptake in the standard of care arm (20-30%, as observed in MU-JHU's program) and Enhanced testing arms (55-66%).

Table 3. Sample size calculations for comparison of proportion of HIV-negative men on PrEP by arm (Aim 1)

Proportion of HIV-negative men	HIV test uptake		Sample size to achieve	
	SOC	Enhanced	80% power	90% power
60%	20%	55%	162	216
60%	20%	65%	103	138
60%	30%	55%	379	508
60%	30%	65%	203	271
70%	20%	55%	133	178
70%	20%	65%	84	112
70%	30%	55%	312	417
70%	30%	65%	165	221

Randomization is 2:1 for Enhanced: SOC. Assumes 95% retention, 80% PrEP uptake

Assuming PrEP uptake in HIV-negative men is 80% and 60% of the men are HIV-uninfected, with a sample size of 500 we would have almost 90% power to detect an increase in PrEP use resulting from a change from 30% to 55% in test uptake. With 500 women, the power for assessing an increase in HIV test uptake exceeds 95% across a range of assumptions in Table 3.

Aim 2: Under the range of assumptions for HIV testing uptake in Aim 1, the overall HIV test uptake will be in the range 43-53% (Table 4) and the number of enrolled women with partners who test and begin ART or PrEP ranges from ~150-200. Assuming power for the causal inference can be approximated by logistic regression, we would have ~80% power to detect an OR of 1.75 or higher, assuming women have 50% ART continuation and viral suppression when male partners do not initiate PrEP or ART. If the number of women with partners who test is between 220-270, we would have approximately 85% power to detect an OR of 1.75.

Table 4. Power approximation for assessing impact of partner PrEP/ART use on women's viral suppression

Overall HIV test uptake	HIV prevalence in male partners	HIV+ men on ART or HIV- men on PrEP	Not on ART or PrEP	OR=1.75	OR=2.0
43%	0.4	147	353	78%	92%
47%	0.3	166	334	81%	94%
50%	0.4	170	330	80%	94%
53%	0.3	189	311	83%	95%

Randomization is 2:1 for Enhanced: SOC. Assumes 95% retention, 80% PrEP uptake and 50% ART persistence

Outcome measurements

Aim 1: Women who are randomized will have key outcomes assessed at scheduled visits. The co-primary outcomes will be HIV testing by the male partner, as measured by questionnaires administered to women in clinic, and PrEP by 6 months after the woman initiated ART. The Kenya pilot indicated minimal bias in self-report of male partner testing. The secondary outcome is PrEP adherence among the male partners who initiate PrEP, based on detectable blood tenofovir levels

at 3 and 6 months after PrEP initiation. PrEP use will also be measured by pharmacy records where men are dispensed PrEP (e.g. at the ANC or Kasangati Couples Center), and self-report through a validated 3-item questionnaire [83]. We will assess HIV seroconversion but expect a low rate.

Aim 2: The exposures of interest are male partner testing, PrEP initiation and ART initiation (Table 2). The primary outcome is the woman's viral load at 12 months post-partum. Viral suppression will be defined as plasma viral load <400 copies/ml). For the secondary outcomes pharmacy records will be used to measure ART dispensation and women will be asked at quarterly visits about treatment interruptions [83]. Secondary outcomes include infant HIV status at 6 weeks (HIV-infected/uninfected) which will be ascertained from ANC records, and infant survival at 12 months as reported by the mother at her 12 month post-partum visit.

Capture of cohort clinical data

Data on male partner HIV testing and female partner ART use and viral load will be obtained from case report forms. Clinic and pharmacy records will be used to document PrEP prescriptions at the Kasangati Couples Center, abstracted in real time from pharmacy records to paper-based case report forms and entered into an electronic database. Automated legal range checks will be programmed to reduce data entry errors and internal quality control reports will be run monthly.

Statistical considerations

Aim 1: The primary analysis will be an intent to treat comparison by randomization arm of the primary outcome: the proportion of women whose male partners who test for HIV and the proportion of HIV-negative men who take PrEP within six months after their HIV-positive partner is randomized. The secondary outcome is tenofovir detection at 3 and 6 months among men who use PrEP.

Aim 2: Our primary analysis will assess the effect of male partner's PrEP or ART use on women's ART continuation and viral suppression at 12 month post-partum period, as the measure of her ART continuation and adherence. This intent of the analysis is to assess the impact of the male partner's current (time-dependent) PrEP or ART use on the women's current ART use and viral suppression. Since initiation of PrEP or ART is secondary to the randomized HIV testing intervention, causal inference methods will be used to assess the impact of male partner HIV testing and PrEP or ART use on post-partum ART continuation. We will calculate standardized-inverse-probability weights with logistic regression [84], to predict the probability of current male PrEP or ART use at each visit as predicted by the instrumental variable HIV testing randomization, and potential time-varying confounders (Table 3), including sexual behavior, future fertility desires, relationship power dynamics, intimate partner violence, alcohol use, and baseline demographics and duration of ART pre-partum. These weights will then be used in a pooled logistic regression model of partners' PrEP or ART exposure as predictors of: 1) ART continuation and 2) viral suppression. In a separate set of models, we will examine the direct effect of male testing, overall and separately for HIV-positive and HIV-negative men, on the woman's ART continuation and viral suppression. We will also explore an instrumental variables approach to causal estimation, given the expected role of randomization in male partners' initiation of PrEP and ART in Aim 1 [85].

DATA SHARING AND OWNERSHIP

During the conduct of the trial, the study database will remain confidential. After study completion, access to data will follow requirements of the Infectious Disease Institute, National Institutes of Health and the University of Washington. The University of Washington International Clinical Research Center has a Manuscripts and Ancillary Studies Committee established to enable data and specimen collaborative work from studies conducted through the research group. Intellectual property and data generated under the proposed project will be administered in accordance with Uganda, University of Washington and NIH policies, including the National Guidelines for Research involving Humans as Research Participants (2014) and the NIH Data Sharing Policy and Implementation Guidance of March 5, 2003.

Materials generated under the project will be disseminated in accordance with University/participating institutional and NIH policies. Depending on such policies, materials may be transferred to others under the terms of a material transfer agreement. Access to databases generated under the project will be available for educational, research and non-profit purposes as approved by the relevant IRBs. Publication of data shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. We will publish our findings in a timely fashion and will present unpublished data at appropriate research conferences. We are committed to collaboration in complex disease research and will participate in data-pooling studies as allowed by our currently established consent forms and IRBs.

Data obtained from this research study are the property of the Infectious Disease Institute of Makerere University and the University of Washington International Clinical Research Center. Local researchers shall have unrestricted access rights to datasets collected through this collaborative research project in accordance with Uganda guidelines.

DISSEMINATION PLAN

Dissemination of study results will follow principles of good participatory practice. Study results will be disseminated through presentations to study participants, stakeholders and policy makers, and published in conference abstracts and peer-reviewed journals. Participants will be informed that if they so desire, they will be contacted at the end of the study for the purpose of informing them about study results. Trial results will also be shared with the community advisory board, the Ministry of Health, implementing partners and civil society groups with interest in reproductive health.

HUMAN SUBJECTS CONSIDERATIONS

The study protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will be reviewed and approved by the IRBs/ECs responsible for oversight of research conducted at the study site. Subsequent to initial review and approval, the responsible IRBs/ECs will review the study at least annually.

Informed consent

Written informed consent will be obtained from each study participant prior to both screening and enrollment. Participants will be offered copies of the informed consent forms. The study site will draft informed consent forms that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all

applicable regulations, based on the consent forms provided in the Appendix. The site will translate the forms into the local language and verify the accuracy of the translation by performing an independent back-translation, which will be reviewed and approved by the International Clinical Research Center at the University of Washington.

Risks

Confidentiality. Although the study site will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as participating in a trial involving HIV-positive persons). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

HIV testing. Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become worried or anxious while waiting for their (or their partner's) HIV test results. Couples-based counseling and discussions of study participation may raise issues between partners, particularly related to blame (from HIV-negative men) and potential termination of the partnership. Participants who learn that they have HIV may experience anxiety or depression related to their test results. Individual and couples-based HIV counseling will be provided by counselors and clinicians who have been trained in specific issues related to HIV serodiscordant couples, including stigma, blame, methods to avoid transmission, and available support services.

Social harm. Intimate Partner Violence (IPV) following HIV status disclosure is an important consideration for couple studies. In a Kenyan study, women who experienced recent IPV were less likely to report partner self-testing (adjusted relative risk ratio [aRRR] 0.10; 95% CI: 0.02-0.47) or couple testing (aRRR 0.13; 95% CI: 0.03-0.54) [86]. Recent partner violence was not significantly associated with male partner self-testing or couple testing. However, couple testing was less likely if the male partner had a neutral or negative reaction to the offer of a self-test (aOR 0.32; 95% CI: 0.12-0.87) or was not easily persuaded to use a self-test (aOR 0.25; 95% CI: 0.09-0.76).

We have extensive experience with counseling >1700 couples over the past decade at the IDI-Kasangati research site. In a study that utilized data from our site, IPV was reported in 2.7% of visits by HIV-infected women and in 2.2% of visits by HIV-uninfected women [87]. In the Partners PrEP Study, HIV-uninfected women in serodiscordant partnerships reported IPV at 0.7% of study visits [88]. Serodiscordant couples perceive PrEP as a solution to the "discordance dilemma" - the desire to avoid HIV acquisition while preserving the relationship. PrEP users benefit from the adherence support of infected partners on ART, and this mutual reinforcement motivates couples who wish to stay together to do so [52].

The majority of women receive support and understanding from their partners when they disclose their HIV status. Fewer than 5% of couples separate or divorce after disclosure of an HIV positive test [89]. A study in South Africa found no evidence that inviting male partners to ANC and HTS increased risk of self-reported IPV in women or men when compared to letters inviting male partners for pregnancy information sessions [36]. Overall, no association between HIV status and IPV was demonstrated in an analysis of data from Demographic and Health Surveys conducted in Kenya, Liberia, Malawi, Mali, Rwanda, Zambia and Zimbabwe [90].

While HIVST studies indicate several benefits and minimal risk of harm, intended or unintended physical, economic, emotional or psychosocial injury could occur before, during or after HIV

testing [91]. Women may experience social harm from partners after discussing and/or performing HIVST. In a Kenyan cohort study, two of 178 pregnant or postpartum women reported verbal abuse following a reactive HIV self-test result [46]. Few instances of violence or harm have been reported in HIVST randomized trials, but these occurred prior to partner notification [92-94], suggesting that HIVST may not directly influence the risk of IPV. This finding is consistent with systematic reviews of harm in studies of HIVST [95], couple testing [96], and other forms of HIV testing [97].

Phlebotomy. Participants may experience discomfort or pain when undergoing phlebotomy. They also may feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle is inserted.

PrEP medication. Risks and side effects related to PrEP include: occurring in a minority of individuals taking PrEP - gastrointestinal intolerance, such as nausea, diarrhea or vomiting, flatulence; rare but serious - lactic acidosis/ severe hepatomegaly with steatosis, renal impairment, including cases of acute renal failure and Fanconi's syndrome (renal tubular injury with severe hypophosphatemia), increase in bone metabolism leading to osteopenia, hypersensitivity reaction.

Qualitative interviews. The risks of participating in the qualitative interviews are minimal. It is possible that participants might become tired during the interview. They may also find some of the questions uncomfortable or hard to answer. In the observation sessions, it is possible that individuals may feel uncomfortable being observed.

Benefits

The primary aim of this study is to evaluate the impact of innovative strategies on male partner HIV testing, engagement in HIV care and prevention among men, and on post-partum ART continuation and adherence among HIV-positive women. HIV prevention practices, according to Ugandan guidelines, will be provided to all participants enrolled in this study. This will include risk reduction counseling, treatment of sexually transmitted infections (STIs), condoms, and referral for medical male circumcision. If prevention strategies are modified during the course of study conduct (e.g. PrEP becomes available through the public health system), participants will be counseled and referred for these strategies as well.

HIV-positive women will benefit from male partner testing, facilitated disclosure and ART counseling. HIV-negative male partner participants will benefit by having free access to PrEP during the study period, until 6 months after their partner initiates ART. Participants may benefit from ongoing access to prevention services. There may be no other direct benefits to participants in this study. However, participants and others also may benefit in the future from information learned from this study.

All participants will be provided with HIV prevention services, including condoms, STI treatment, and ongoing support, including counseling and referral to other support services.

Care for HIV-positive male partners

This study will identify male partners who are infected with HIV, either as part of testing male partners of unknown status, or during follow-up of initially HIV-negative men. Study staff will provide participants with their HIV test results in the context of post-test counseling. Men identified as HIV-positive will be referred for HIV clinical care, including primary care and antiretroviral

therapy, according to Ugandan guidelines. During the course of the study, it is possible that guidelines will change regarding clinical care of persons with HIV (including optimal therapy, prophylaxis, etc.). At all times during the study, treatment and referral practices for HIV-positive persons in the study will adhere to national ART guidelines. After the study ends, HIV-positive participants will be provided referrals to other care programs for ongoing HIV primary care. This type of care will also be offered to initially HIV-negative study participants who become infected during follow-up.

Benefits to the community

An important goal of this study is to achieve the study objectives in a way that provides benefits to the community that endure beyond the proposed study lifetime regardless of the specific outcome of the study. Some of these community benefits are listed below:

Couples HIV counseling and testing (CHCT): Infrastructure to effectively counsel and test couples for HIV will be needed for this study to effectively recruit male partners. CHCT capacity developed at the study site in collaboration with existing local VCT programs through training of local counselors is a beneficial resource to the community well after the study is completed. Given recent data that 70% of incident HIV cases are transmitted from regular partners, creating awareness, increasing demand, providing couples VCT and providing ART and PrEP will reduce transmission of HIV among couples. This will have consequent benefits to the family and community by maintaining one healthy partner.

Development of male-friendly HIV testing and linkage to HIV care and prevention within real world PMTCT B+ settings: This study aims to provide HIV prevention policy makers with information on how to best engage male partners in PMTCT B+ programs. In addition to the provision of this biomedical method, the study site will provide CHCT, and routine adherence counseling. The outcome of the study will be evidence upon which to based policy guidelines for improving male involvement in PMTCT in Uganda and nearby countries with similar HIV prevention needs.

Treatment for injury

If a study participant is injured while participating in this study, they will be offered care at the study clinic, free of charge until their injury is cured or stabilizes. Participants will be encouraged to tell members of the team of researchers if they feel they have been injured because of taking part in this study. Those who require medical care that the study clinic cannot provide will be referred by the study doctors to the appropriate services or organizations that can provide care for the injury. This referral will be covered by the University of Washington comprehensive liability program.

Study records

Site Investigators will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. The investigator will retain all study records for at least five years after completion of the study. Study records include administrative documentation and regulatory documentation as well as documentation related to each participant screened and/or enrolled in the study, including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents. Logs linking

participant name to study identification number and other identifying information in study files will be retained for five years after the study is completed; after that time, the link will be destroyed. Participants may consent to storage of samples for future research; any future research must be approved by overseeing Institutional Review Boards.

Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent possible. Personal identifying information will be retained at the study site. The study site will establish a standard operating procedure for confidentiality protection that reflects the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at the study site.

All study-related information will be stored securely at the study site. All participant information will be stored in areas with limited access. Data collection, administrative forms, laboratory specimens, and other reports will be identified only by a coded number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participants' study information will not be released without their written permission, except as necessary for oversight by:

The University of Washington
Harvard Medical School
The United States National Institutes of Health
Uganda Ministry of Health
The National HIV/AIDS Research Committee of the Uganda National Council for Science and Technology
The Uganda National Council of Science and Technology (UNCST)
The Uganda National Drug Authority

Table 5. Procedures for HIV-positive pregnant women

	ANTENATAL					POSTNATAL			
	T1	**T2**	**T3**	**T4**	**Del**	**M3**	**M6**	**M9**	**M12**
ADMINISTRATIVE AND REGULATORY PROCEDURES									
Obtain written informed consent	[X]	[X]	[X]	[X]					
Assign participant identification number	[X]	[X]	[X]	[X]					
Assess eligibility	[X]	[X]	[X]	[X]					
Collect/update locator information	[X]	[X]	[X]	[X]		X	X	X	X
Collect/update demographic information	[X]	[X]	[X]	[X]					
Obtain random allocation	[X]	[X]	[X]	[X]					
Schedule next visit	[X]	[X]	[X]	[X]		X	X	X	
COUNSELING									
HIV/STI risk reduction counseling, condom provision	[X]	[X]	[X]	[X]		X	X	X	X
Counseling (ART adherence, clinical & prevention benefits)	[X]	[X]	[X]	[X]		X	X	X	X
CLINICAL PROCEDURES									
Provide HIV test results	[X]	[X]	[X]	[X]					
Medical history	[X]	[X]	[X]	[X]		X	X	X	X
Perform physical exam	[X]	[X]	[X]	[X]		[X]	[X]	[X]	[X]
STI syndromic assessment and management	[X]	[X]	[X]	[X]		[X]	[X]	[X]	[X]
Referral for / provision of ART according to national guidelines	[X]	[X]	[X]	[X]		X	X	X	X
PMTCT PROCEDURES*									
Antenatal care package	[X]	[X]	[X]	[X]					
Postnatal care package						[X]	[X]	[X]	[X]
Infant HIV status at 6 weeks						X			
Infant survival at 12 months post-partum									X
LABORATORY PROCEDURES									
Syphilis testing	X	[X]	[X]	[X]					
HIV serology	X	[X]	[X]	[X]					
Plasma HIV viral load							X		X

*Standard of care

Study staff will perform study specific procedures at collaborating clinics

LEGEND

[ ] as indicated

T = trimester

Del = delivery

Table 6. Procedures for male partners

	E	M3*	M6	M9	M12
ADMINISTRATIVE AND REGULATORY PROCEDURES					
Obtain written informed consent					
CLINIC PROCEDURES					
Confirmatory testing (self-test arm)	X				
Initial testing (invitation letter arm)	X				
Provide HIV test results and post-test counseling	X				
Medical history	X	X	X	X	X
Perform physical exam	X	[X]	[X]	[X]	[X]
STI syndromic assessment and management	X	[X]	[X]	[X]	[X]
Syphilis testing	X				
HIV-NEGATIVE MEN					
Provide HIV test results		X	X	X	X
Hepatitis B surface antigen	X				
Creatinine	X		X		[X]
PrEP provision	X	X	X	[X]	[X]
HIV-POSITIVE MEN					
Referral for / provision of ART according to national guidelines	X	X	X	X	X
Assess ART use and linkage/retention in care		X	X	X	X
Plasma HIV viral load	X		X		[X]

[ ] as indicated
*Three months after study enrollment

Table 7. Procedures for HIV seroconverters among HIV-negative male partners who initiate PrEP

	Possible seroconversion visit (≥1 rapid HIV test positive)	Follow-up to possible seroconversion (ideally within one month of possible seroconversion)	M3	M6
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY PROCEDURES				
Provide HIV counseling, including couples counseling	X	X	X	X
CLINICAL PROCEDURES				
Collect medical history	X	X		X
Perform physical exam	X		X	X
Collect blood specimen	X	X	X	X
Stop PrEP, if applicable	X			
Provide test results	X	X		
Refer for HIV care		X		
Assess linkage to care			X	X
LABORATORY PROCEDURES				
CD4 count	X	X	X	X
HIV plasma viral load	X	X	X	X
HIV serology (confirmatory EIA)	X			
Serum, plasma archive for HIV resistance assays, PrEP levels (batched testing)	X	X	X	X

HIV-negative men who seroconvert to HIV will have one set of samples collected as close in time to the seroconversion visit as possible (ideally, either at the SC or SC<1 month visits). Samples to be collected are:

CD4 count
Viral load
Plasma archive (for tenofovir and resistance assays)

REFERENCES

1. Mugwanya K, Heffron R, Wyatt C, et al. Optimizing the frequency of kidney safety monitoring in HIV-uninfected persons using daily oral tenofovir disoproxil fumarate PrEP. 2016 AIDS, 21st International AIDS Conference. Durban, South Africa, **2016**:Abstract FRAE0106LB.

2. Wyatt M A, Pisarski EE, Tam M, et al. Experiences of PrEP discontinuation in African HIV serodiscordant couples: Qualitative results from the Partners Demonstration Project. AIDS 2016: 21st International AIDS Conference. Durban, South Africa, **2016**:Abstract FRAE0103.

3. Beyrer C, Birx DL, Bekker LG, et al. The Vancouver Consensus: antiretroviral medicines, medical evidence, and political will. Lancet **2015**; 386:505-7.

4. UNAIDS. The Gap Report. Available at: http://www.unaids.org/en/resources/documents/2014/20140716_UNAIDS_gap_report.

5. Uganda AIDS Commission. HIV and AIDS Uganda country progress report; 2013. Kampala, **2014**.

6. Kim MH, Ahmed S, Buck WC, et al. The Tingathe programme: a pilot intervention using community health workers to create a continuum of care in the prevention of mother to child transmission of HIV (PMTCT) cascade of services in Malawi. J Int AIDS Soc **2012**; 15 Suppl 2:17389.

7. INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med **2015**; 373:795-807.

8. Stranix-Chibanda L, Brummel S, Angelidou K, et al. Low acceptance of early antiretroviral therapy (ART) among post-partum women enrolled in IMPAACT PROMISE studies across the globe. 21st International AIDS Conference (AIDS 2016). Durban, South Africa **2016**:Abstract THAB0106LB.

9. Currier J, Britto P, Hoffman R, et al. Randomized trial of stopping or continuing ART among postpartum women with pre-ART CD4 > 400 cells/mm3 (PROMISE 1077HS). AIDS 2016: 21st International AIDS Conference. Durban, South Africa, **2016**:Abstract THAB0103LB.

10. Mujugira A, Baeten J, Kidoguchi L, et al. Sustained viral suppression among East African HIV-infected members of serodiscordant couples initiating ART with high CD4 counts and during pregnancy 11th International Conference on HIV Treatment and Prevention Adherence (Adherence 2016). Fort Lauderdale, Florida, USA, **2016**:Abstract 43.

11. Johnson L, Rehle T, Jooste S, Bekker L. Rates of HIV testing and diagnosis in South Africa: successes and challenges. AIDS **2015**; 29:401-9.

12. Bicego GT, Nkambule R, Peterson I, et al. Recent patterns in population-based HIV prevalence in Swaziland. PLoS One **2013**; 8:e77101.

13. Morfaw F, Mbuagbaw L, Thabane L, et al. Male involvement in prevention programs of mother to child transmission of HIV: a systematic review to identify barriers and facilitators. Systematic reviews **2013**; 2:5.

14. Farquhar C, Kiarie JN, Richardson BA, et al. Antenatal couple counseling increases uptake of interventions to prevent HIV-1 transmission. J Acquir Immune Defic Syndr **2004**; 37:1620-6.

15. Desgrees-Du-Lou A, Brou H, Djohan G, et al. Beneficial effects of offering prenatal HIV counselling and testing on developing a HIV preventive attitude among couples. Abidjan, 2002-2005. AIDS Behav **2009**; 13:348-55.

16. Maman S, Mbwambo J, Hogan NM, Kilonzo GP, Sweat M. Women's barriers to HIV-1 testing and disclosure: challenges for HIV-1 voluntary counselling and testing. AIDS Care **2001**; 13:595-603.

17. Baiden F, Remes P, Baiden R, et al. Voluntary counseling and HIV testing for pregnant women in the Kassena-Nankana district of northern Ghana: is couple counseling the way forward? AIDS Care **2005**; 17:648-57.

18. Bajunirwe F, Muzoora M. Barriers to the implementation of programs for the prevention of mother-to-child transmission of HIV: a cross-sectional survey in rural and urban Uganda. AIDS Res Ther **2005**; 2:10.

19. Peltzer K, Mosala T, Dana P, Fomundam H. Follow-up survey of women who have undergone a prevention of mother-to-child transmission program in a resource-poor setting in South Africa. J Assoc Nurses AIDS Care **2008**; 19:450-60.

20. Msuya SE, Mbizvo EM, Hussain A, Uriyo J, Sam NE, Stray-Pedersen B. Low male partner participation in antenatal HIV counselling and testing in northern Tanzania: implications for preventive programs. AIDS Care **2008**; 20:700-9.

21. de Paoli MM, Manongi R, Klepp KI. Counsellors' perspectives on antenatal HIV testing and infant feeding dilemmas facing women with HIV in northern Tanzania. Reproductive health matters **2002**; 10:144-56.

22. de Paoli MM, Manongi R, Klepp KI. Factors influencing acceptability of voluntary counselling and HIV-testing among pregnant women in Northern Tanzania. AIDS Care **2004**; 16:411-25.

23. Brou H, Djohan G, Becquet R, et al. When do HIV-infected women disclose their HIV status to their male partner and why? A study in a PMTCT programme, Abidjan. PLoS Med **2007**; 4:e342.

24. Tijou Traore A, Querre M, Brou H, Leroy V, Desclaux A, Desgrees-du-Lou A. Couples, PMTCT programs and infant feeding decision-making in Ivory Coast. Soc Sci Med **2009**; 69:830-7.

25. Ambia J, Mandala J. A systematic review of interventions to improve prevention of mother-to-child HIV transmission service delivery and promote retention. J Int AIDS Soc **2016**; 19:20309.

26. Aluisio AR, Bosire R, Betz B, et al. Male Partner Participation in Antenatal Clinic Services is Associated with Improved HIV-free survival Among Infants in Nairobi, Kenya: A Prospective Cohort Study. J Acquir Immune Defic Syndr **2016**.

27. Chandisarewa W, Stranix-Chibanda L, Chirapa E, et al. Routine offer of antenatal HIV testing ("opt-out" approach) to prevent mother-to-child transmission of HIV in urban Zimbabwe. Bull World Health Organ **2007**; 85:843-50.

28. Katz DA, Kiarie JN, John-Stewart GC, Richardson BA, John FN, Farquhar C. Male perspectives on incorporating men into antenatal HIV counseling and testing. PLoS One **2009**; 4:e7602.

29. Larsson EC, Thorson A, Nsabagasani X, Namusoko S, Popenoe R, Ekstrom AM. Mistrust in marriage--reasons why men do not accept couple HIV testing during antenatal care- a qualitative study in eastern Uganda. BMC Public Health **2010**; 10:769.

30. Theuring S, Mbezi P, Luvanda H, Jordan-Harder B, Kunz A, Harms G. Male involvement in PMTCT services in Mbeya Region, Tanzania. AIDS Behav **2009**; 13 Suppl 1:92-102.

31. Reece M, Hollub A, Nangami M, Lane K. Assessing male spousal engagement with prevention of mother-to-child transmission (pMTCT) programs in western Kenya. AIDS Care **2010**; 22:743-50.

32. Byamugisha R, Tumwine JK, Semiyaga N, Tylleskar T. Determinants of male involvement in the prevention of mother-to-child transmission of HIV programme in Eastern Uganda: a cross-sectional survey. Reproductive health **2010**; 7:12.

33. Orne-Gliemann J, Tchendjou PT, Miric M, et al. Couple-oriented prenatal HIV counseling for HIV primary prevention: an acceptability study. BMC Public Health **2010**; 10:197.

34. Falnes EF, Moland KM, Tylleskar T, de Paoli MM, Msuya SE, Engebretsen IM. "It is her responsibility": partner involvement in prevention of mother to child transmission of HIV programmes, northern Tanzania. J Int AIDS Soc **2011**; 14:21.

35. Osoti AO, John-Stewart G, Kiarie J, et al. Home visits during pregnancy enhance male partner HIV counselling and testing in Kenya: a randomized clinical trial. AIDS **2014**; 28:95-103.

36. Mohlala BK, Boily MC, Gregson S. The forgotten half of the equation: randomized controlled trial of a male invitation to attend couple voluntary counselling and testing. AIDS **2011**; 25:1535-41.

37. Nyondo AL, Choko AT, Chimwaza AF, Muula AS. Invitation cards during pregnancy enhance male partner involvement in prevention of mother to child transmission (PMTCT) of human immunodeficiency virus (HIV) in Blantyre, Malawi: a randomized controlled open label trial. PLoS One **2015**; 10:e0119273.

38. Byamugisha R, Astrom AN, Ndeezi G, Karamagi CA, Tylleskar T, Tumwine JK. Male partner antenatal attendance and HIV testing in eastern Uganda: a randomized facility-based intervention trial. J Int AIDS Soc **2011**; 14:43.

39. Semrau K, Kuhn L, Vwalika C, et al. Women in couples antenatal HIV counseling and testing are not more likely to report adverse social events. AIDS **2005**; 19:603-9.

40. Homsy J, Kalamya JN, Obonyo J, et al. Routine intrapartum HIV counseling and testing for prevention of mother-to-child transmission of HIV in a rural Ugandan hospital. J Acquir Immune Defic Syndr **2006**; 42:149-54.

41. Napierala Mavedzenge S, Baggaley R, Corbett EL. A review of self-testing for HIV: research and policy priorities in a new era of HIV prevention. Clin Infect Dis **2013**; 57:126-38.

42. Johnson C, Baggaley R, Forsythe S, et al. Realizing the potential for HIV self-testing. AIDS Behav **2014**; 18 Suppl 4:S391-5.

43. Figueroa C, Johnson C, Verster A, Baggaley R. Attitudes and Acceptability on HIV Self-testing Among Key Populations: A Literature Review. AIDS Behav **2015**; 19:1949-65.

44. Choko AT, Taegtmeyer M, MacPherson P, et al. Initial accuracy of HIV rapid test kits stored in suboptimal conditions and validity of delayed reading of oral fluid tests. PLoS One **2016**; 11:e0158107.

45. Choko AT, Desmond N, Webb EL, et al. The uptake and accuracy of oral kits for HIV self-testing in high HIV prevalence setting: a cross-sectional feasibility study in Blantyre, Malawi. PLoS Med **2011**; 8:e1001102.

46. Thirumurthy H, Masters SH, Mavedzenge SN, Maman S, Omanga E, Agot K. Promoting male partner HIV testing and safer sexual decision making through secondary distribution of self-tests by HIV-negative female sex workers and women receiving antenatal and post-partum care in Kenya: a cohort study. The lancet HIV **2016**; 3:e266-74.

47. Agot K, Obonyo B, Masters S, Maman S, Napierala Mavedzenge S, Thirumurthy H. Promoting male partner and couples testing through secondary distribution of self-tests by pregnant and postpartum women: a randomized trial. AIDS 2016, 21st International AIDS Conference Durban, South Africa, **2016**:Abstract FRAC0104.

48. Kieffer MP, Mattingly M, Giphart A, et al. Lessons learned from early implementation of option B+: the Elizabeth Glaser Pediatric AIDS Foundation experience in 11 African countries. J Acquir Immune Defic Syndr **2014**; 67 Suppl 4:S188-94.

49. 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**; 371:2183-91.

50. Piot P, Bartos M, Larson H, Zewdie D, Mane P. Coming to terms with complexity: a call to action for HIV prevention. Lancet **2008**; 372:845-59.

51. Lingappa JR, Kahle E, Mugo N, et al. Characteristics of HIV-1 discordant couples enrolled in a trial of HSV-2 suppression to reduce HIV-1 transmission: the partners study. PLoS One **2009**; 4:e5272.

52. 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**; 59:463-8.

53. Ngure K, Mugo N, Celum C, et al. A qualitative study of barriers to consistent condom use among HIV-1 serodiscordant couples in Kenya. AIDS Care **2012**; 24:509-16.

54. Ngure K, Shell-Duncan B, Curran K, et al. Following the doctor's advice: Experiences of HIV serodiscordant couples enrolled in a PrEP demonstration project in Kenya. HIV Research for Prevention (HIV R4P) Meeting. Cape Town, South Africa:, **2014. Abstract P46.06**.

55. Ware NC, Idoko J, Kaaya S, et al. Explaining adherence success in sub-Saharan Africa: an ethnographic study. PLoS Med **2009**; 6:e11.

56. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med **2011**; 365:493-505.

57. Mujugira A, Celum C, Coombs RW, et al. HIV Transmission Risk Persists During the First 6 Months of Antiretroviral Therapy. J Acquir Immune Defic Syndr **2016**; 72:579-84.

58. Mujugira A, Celum C, Thomas KK, et al. Delay of antiretroviral therapy initiation is common in East African HIV-infected individuals in serodiscordant partnerships. J Acquir Immune Defic Syndr **2014**; 66:436-42.

59. Baeten J, 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 Med **2016**; 13:e1002099.

60. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med **2012**; 367:399-410.

61. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med **2010**; 363:2587-99.

62. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med **2012**; 367:423-34.

63. 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. Lancet **2013**; 381:2083-90.

64. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV: World Health Organization, **2015**:78.

65. Ministry of Health, Kenya, Guidelines on use of antiretrovirals for treating and preventing HIV infection in Kenya, **2016**.

66. 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**; 62:399-47.

67. Murnane PM, Celum C, Mugo N, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS **2013**; 27:2155-60.

68. Baeten J, Heffron R, Kidoguchi L, et al. Near elimination of HIV transmission in a demonstration project of PrEP and ART. CROI 2015: Conference on Retroviruses and Opportunistic Infections. Seattle, WA, USA, **2015**:Abstract 24.

69. Ngure K, Heffron R, Mugo N, et al. Uptake of HIV self-testing among people receiving PrEP in Kenya. HIV Research for Prevention (HIV R4P) Meeting. Cape Town, South Africa, **2014**:Abstract O127.02.

70. National HIV Testing Services Policy and Implementation Guidelines. In: Health Mo, ed. Kampala, Uganda, **2016**.

71. Consolidated Guidelines on the Prevention and Treatment of HIV in Uganda. Kampala, Uganda: Ministry of Health, **2016**.

72. 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. Lancet Infect Dis **2014**; 14:1055-64.

73. Uganda National Policy Guidelines for HIV Counseling and Testing. In: Health Mo, ed. Kampala, Uganda, **2005**.

74. Curran K, Ngure K, Shell-Duncan B, et al. 'If I am given antiretrovirals I will think I am nearing the grave': Kenyan HIV serodiscordant couples' attitudes regarding early initiation of antiretroviral therapy. AIDS **2014**; 28:227-33.

75. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med **2012**; 367:399-410.

76. Kalichman SC, Simbayi LC, Cloete A, Mthembu PP, Mkhonta RN, Ginindza T. Measuring AIDS stigmas in people living with HIV/AIDS: the Internalized AIDS-Related Stigma Scale. AIDS Care **2009**; 21:87-93.

77. Straus M, Hamby S, Boney-McCoy S, Sugarman D. Measuring sexual relationship power in HIV/STD research. J Fam Issues **1996**; 17:283-316.

78. Cherpitel CJ, Ye Y, Bond J, et al. Cross-national performance of the RAPS4/RAPS4-QF for tolerance and heavy drinking: data from 13 countries. J Stud Alcohol **2005**; 66:428-32.

79. Mahenge B, Likindikoki S, Stockl H, Mbwambo J. Intimate partner violence during pregnancy and associated mental health symptoms among pregnant women in Tanzania: a cross-sectional study. BJOG **2013**; 120:940-6.

80. Erlen JA, Cha ES, Kim KH, Caruthers D, Sereika SM. The HIV Medication Taking Self-efficacy Scale: Psychometric evaluation. J Adv Nurs **2010**; 66:2560-72.

81. Adler PA, Adler P. Observational techniques. In: Handbook of Qualitative Research, ed by Denzin, NK & Lincoln, YS. Thousand Oaks, London, New Delhi: Sage Publishing, **1994**:377-92.

82. Elo S, Kyngas H. The qualitative content analysis process. J Adv Nurs **2008**; 62:107-15.

83. Wilson IB, Lee Y, Michaud J, Fowler FJ, Jr., Rogers WH. Validation of a New Three-Item Self-Report Measure for Medication Adherence. AIDS Behav **2016**; 20:2700-8.

84. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol **2008**; 168:656-64.

85. Angrist J, Imbens G, Rubin D. Identification of causal effects using instrumental variables. J Am Stat Assoc **1996**; 91:444-55.

86. Schaffer E, Agot K, Thirumurthy H. Role of partner violence in women's ability to distribute self-tests to male partners. Conference on Retroviruses and Opportunisitc Infections. Seattle, Washington, **2017**.

87. Were E, Curran K, Delany-Moretlwe S, et al. A prospective study of frequency and correlates of intimate partner violence among African heterosexual HIV serodiscordant couples. AIDS **2011**; 25:2009-18.

88. Roberts ST, Haberer J, Celum C, et al. Intimate Partner Violence and Adherence to HIV Pre-exposure Prophylaxis (PrEP) in African Women in HIV Serodiscordant Relationships: A Prospective Cohort Study. J Acquir Immune Defic Syndr **2016**; 73:313-22.

89. Nebie Y, Meda N, Leroy V, et al. Sexual and reproductive life of women informed of their HIV seropositivity: a prospective cohort study in Burkina Faso. J Acquir Immune Defic Syndr **2001**; 28:367-72.

90. Harling G, Msisha W, Subramanian SV. No association between HIV and intimate partner violence among women in 10 developing countries. PLoS One **2010**; 5:e14257.

91. World Health Organization. Guidelines on HIV self-testing and partner notification. Geneva, **2016**.

92. Brown LB, Miller WC, Kamanga G, et al. HIV partner notification is effective and feasible in sub-Saharan Africa: opportunities for HIV treatment and prevention. J Acquir Immune Defic Syndr **2011**; 56:437-42.

93. Rosenberg NE, Mtande TK, Saidi F, et al. Recruiting male partners for couple HIV testing and counselling in Malawi's option B+ programme: an unblinded randomised controlled trial. The lancet HIV **2015**; 2:e483-91.

94. Cherutich P, Golden MR, Wamuti B, et al. Assisted partner services for HIV in Kenya: a cluster randomised controlled trial. The lancet HIV **2016**.

95. Brown AN, Djimeu EW, Cameron DB. A review of the evidence of harm from self-tests. AIDS Behav **2014**; 18 Suppl 4:S445-9.

96. World Health Organization. Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: recommendations for a public health approach. Geneva, Switzerland, **2012**.

97. WHO. Annex 21: Review of the social harm reported in standard HIV testing services and those reported in HIV self-testing. Geneva, **2016**.