PROTOCOL

Interventions for Improved Post-partum ART Continuation and HIV Testing of Male Partners of Women in PMTCT B+ in Uganda (Kingasa Study)

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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
COVID-19	Coronavirus disease 2019
DNA	Deoxyribose Nucleic Acid
EID	Early Infant Diagnosis
FTC/TDF	Co-formulated Emtricitabine-Tenofovir Disoproxil Fumarate
HEI	HIV Exposed Infants
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
PCR	Polymerase Chain Reaction
PWLHIV	Pregnant women Living with HIV
PMTCT	Prevention of Mother-To-Child HIV Transmission
POC	Point of Care
PrEP	Pre-Exposure Prophylaxis
PST	Problem Solving Therapy
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
VL	Viral Load
VS	Viral Suppression
WHO	World Health Organization

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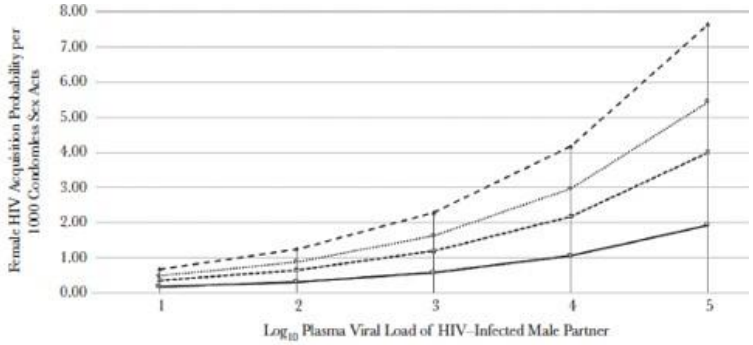
SUMMARY

Uganda has the seventh highest HIV burden globally and one of the highest fertility rates in Africa. African women have 3-4 fold higher risk of HIV acquisition during late pregnancy and the postpartum period, based on risk per unprotected coital act, compared to when women are not pregnant and adjusted for their partner's viral load [figure 1]. Additionally, prevention of mother-to-child HIV transmission Option B+ (PMTCT B+) is national policy in Uganda (2). 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.

Figure 1: Increased HIV acquisition risk per-sex act in pregnancy and post-partum (1)



Nonpregnant	0.17	0.31	0.58	1.05	1.93
Early pregnancy	0.36	0.65	1.19	2.19	4.00
Late pregnancy	0.48	0.89	1.62	2.97	5.44
Postpartum	0.68	1.25	2.29	4.18	7.65

Innovative approaches are needed to address the challenges associated with male partner engagement during their partner's antenatal and postpartum care. Men are less likely to engage in HIV services, resulting in poor clinical outcomes. This lack of engagement affects women's retention in the HIV treatment cascade, which subsequently affects prevention of mother-to-child HIV transmission and infant survival. Barriers to male partner involvement include fear of knowing one's status, stigma (3, 4), men's belief that their status is the same as their partners (i.e., testing by 'proxy') (5), cultural norms that men should not accompany their wives to antenatal care (6), negative attitudes of health care workers (7, 8) (i.e., not allowing men in antenatal clinics) (4, 7, 9), and men's concern about time away from work and the impact on their income (4, 8-11). A key question in the field is how to strengthen male partner engagement and motivate men to test for HIV. By understanding the barriers and key motivations of linkage to care, we can improve uptake of prevention and care services for men, thus impacting the HIV care continuum for their female partners.

In our ongoing study, Obumu (*R01 MH113434*) we are evaluating the impact of secondary distribution of HIV self-testing on male partner engagement in HIV testing, and uptake in HIV care and prevention services. In this evaluation, women were randomized to the intervention arm by providing their partner an HIVST kit, *or* the control arm, by providing a standard of care letter provided by the clinic. Though qualitative data and informal focus group discussions with men in Obumu, we have learned that disclosure is a major barrier to secondary distribution of HIV self-testing kits from HIV-positive pregnant women to their male partners. We have conducted in-depth interviews and focus group discussions of male partners of pregnant women as part of Obumu, and many men indicate they will be motivated to test for HIV at the ANC clinic if other services are offered, such as syphilis testing and other health services (e.g., blood pressure and visual acuity screening) provided during a wellness visit. We hypothesize that if HIV testing is offered in conjunction with an emphasis on syphilis testing, blood pressure, an eye exam, and COVID-19 symptom screening, this may offset the barriers to either responding to an invitation letter for HIV testing or use of HIV the self-test provided by their female partner and improve their overall uptake of testing for HIV.

By leveraging the findings from Obumu, we propose to enroll a new cohort of 200 HIV-positive pregnant

women with partners of unknown status in order to evaluate whether an invitation to a wellness screening, including dual rapid syphilis and HIV tests, blood pressure, visual acuity screening, COVID-19 symptom screening will overcome male partners reluctance to be tested only for HIV in PMTCT clinics.

Pregnant women in PMTCT do not always have viral load tests obtained or counseling about their results. In the Obumu study, we have found that approximately 30% of women living with HIV did not have a viral load result at months 6-12 post-partum, and of those who did have a viral load obtained, 20% were not virally suppressed. The proportion of post-partum women in Obumu without a viral load increased to over 40% after the COVID-19 shut down, which adds another barrier to ART adherence counseling among women who are facing other challenges with ART continuation after delivery. This could lead to increased risk of breastmilk transmission for women who are not virally suppressed.

The recent results of the STREAM study in South Africa indicate that point-of-care (POC) HIV viral load (VL) testing and same day ART adherence counseling increased viral suppression and retention in care by 14%.(12) The costs of POC VL are less than standard laboratory-based VL assays, providing a cost-effective strategy if it is associated with a higher rate of viral suppression in pregnant and post-partum women, as was found in the STREAM study.

The COVID-19 emergency and requirements around sheltering at home may have increased the potential for prepartum ART non-adherence and post-partum ART drop-out due to greater fears of unintended HIV status disclosure, increased risk of gender-based violence, alcohol and substance use, and heightened stress and anxiety. Point-of-care HIV viral load testing, coupled with same day ART adherence counseling may address the psychosocial barriers to ART, thus improve ART use in this population.

In the Kingasa study, we will use a factorial design in order to evaluate both an intervention to increase male partner HIV testing and an intervention for pregnant and postpartum women living with HIV to provide real-time HIV VL load and ART adherence counseling. Specifically, we will evaluate a) whether invitations to wellness visits increase the proportion of male partners who test for HIV and b) whether POC HIV VL tests increase viral suppression among pregnant and postpartum women living with HIV. We will also assess the impact of providing male counselor phone call follow-up to men in the wellness visit arm to encourage linkage to HIV care and prevention after HIV testing. Women will be randomized 1:1:1:1 to receive a) standard of care interventions with an invitation letter for male partners for fast-track visit for HIV testing and laboratory HIV testing for women at enrollment and every 6 months until 12 months postpartum, b) invitation letter for male partners for fast track visit for HIV testing and POC VL tests for women at enrollment and every 6 months until 12 months postpartum; c) invitation letter to male partners for wellness visits and laboratory-based HIV VL testing for women at enrollment and every 6 months until 12 months postpartum; and d) invitation letter to male partners for wellness visits and POC viral load testing for women at enrollment and every 6 months until 12 months post-partum. Women who are randomized to receive POC VL will receive same day ART adherence counseling and those randomized to receive lab based VL will receive VL results at their next visit with ART adherence counseling based on their VL results.

Women in both arms will receive counseling to minimize social harms associated with status disclosure and HIV testing, and additional counseling and referral to social support services when social harms occur. Based on the current Ugandan MOH guidelines to offer HIVST to both HIV-positive and HIV-negative pregnant women in ANC clinics, women in both arms will be provided an HIVST to give to their partner if they choose. They will be trained in the use and interpretation of the HIVST and be given information about HIV testing and prevention and care services, which she will give to her partner.

This study has been designed to address the gap in male partner engagement by using innovative methods to link men to HIV testing, prevention and care, and thus PMTCT outcomes for women.

Design: Randomized clinical trial
Up to 6 months of post-partum follow-up

Population: 200 HIV-positive pregnant women who have a partner of unknown status and their male partners

Study Site: The Infectious Diseases Institute (IDI) Kasangati and Kitebi Health Center III antenatal care (ANC) clinic in Kampala, Uganda

Approach: We will recruit pregnant women ≥18 years accessing ANC and PMTCT B+ programs in Kampala, who have a male partner of unknown HIV status. Women will be randomized 1:1:1:1 to the intervention for male partners (provision of an invitation letter for a wellness visit with dual rapid syphilis and HIV tests, blood pressure, visual acuity screening and COVID-19 symptom screening or an invitation letter for fast track testing at the clinic (the standard of care), and either the intervention of POC VL and same day ART adherence counseling or the standard of care every six months lab-based HIV VL testing. with adherence counseling at their next visit.

In accordance with MOH guidelines, women in both arms will be offered an HIVST to bring home to their partners. In both arms, women will be instructed in the use and interpretation of HIVST and be provided up to two HIVST kits to give to or use with their male partners, per Ugandan Ministry of Health guidelines. After HIV testing and enrollment into the Kingasa study, HIV-negative male partners will be offered PrEP and HIV-positive men will be linked to ART. We will recommend that HIV-negative men take PrEP until their partner has been on ART for at least 6 months or longer if they report additional partners of unknown status.

Aim 1: To evaluate whether the proportion of male partners of pregnant HIV-positive women who test for HIV, is improved after distribution of a letter of invitation to a wellness visit (dual syphilis and HIV rapid test, blood pressure, visual acuity screening and COVID-19 screening) to their female partners compared to the standard of care (standard of care invitation letter from the clinic).

Aim 2: To evaluate whether POC viral load testing with same day ART adherence support improves viral suppression among pregnant and post-partum women living with HIV compared to standard of care lab-based HIV VL testing.

Aim 3: To assess the proportion of HIV-negative male partners who initiate PrEP and HIV positive men who initiate ART among male partners who test for HIV and are provided male counselor phone follow up or who receive standard of care.

Aim 4: To evaluate acceptability and preferences for HIV testing and other health services among pregnant women and male partners using mixed methods.

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) (16). 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 (17). Uganda carries the seventh highest HIV burden in the world, with 1.4 million people living with HIV, and 53,000 new infections and 23,000 AIDS-related deaths in 2018 (18). Uganda also has a high fertility rate (5.4 children per woman in 2016) (19). A key driver of HIV incidence in Uganda is low utilization of antenatal and delivery services (20). HIV-positive women are more likely to complete the PMTCT cascade when male partners are tested and engaged in care (21). To have a greater impact of PMTCT B+ and ANC programs 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, post-partum ART continuation among HIV-positive women, and PrEP uptake among HIV-negative pregnant women with an HIV-positive partner or partner who refuses to test.

Rationale for increasing HIV testing among male partners of HIV-positive pregnant women

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 (22, 23). 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 (6). 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 (21). Male partner involvement increases condom use (24, 25), women's utilization of antenatal services and HIV testing (26-28), obtaining HIV results (29), ART use (24, 29, 30), adherence to infant feeding advice (5, 31-33), infant HIV testing (34), and infant HIV-free survival (34, 35). Despite these multiple benefits, studies from Africa have found that male partner testing rates remain low (16-54%) (3, 24, 30, 36). Barriers to male partner involvement include fear of knowing one's status, stigma (3, 4), men's belief that their status is the same as their partners (i.e., testing by 'proxy') (5), cultural norms that men should not accompany their wives to antenatal care (6), negative attitudes of health care workers (7, 8) (i.e., not allowing men in antenatal clinics) (4, 7, 9), and men's concern about time away from work and the impact on their income (4, 8-11).

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 (6). However, partner return following receipt of official invitation letters is not high – 36% in Kenya (37), 26-35% in South Africa (38), 28% in Malawi (39) and 16% in Uganda (40). Couples HIV testing and counseling improves uptake of HIV testing and ART without increased risk of social harm, compared with individual counseling (24, 41).

Other approaches include offering ANC services for couples during weekends or non-working hours (6) and intra-partum HIV testing and counseling (42). Couples testing, flexible hours, expedited clinic processing for women who bring male partners (42), male support groups (8) and peer sensitization of men (4) modestly increased male partner involvement in some PMTCT programs, but have not achieved substantially large increases in partner testing.

Strategies to increase HIV testing of male partners of pregnant women

1) MOH roll out of secondary distribution of HIVST to pregnant women

One strategy to increase HIV testing of male partners is HIV self-testing. HIV self-testing is being rolled out in Kampala by The President's Emergency Plan for AIDS Relief (PEPFAR) partners coordinated by

the Ministry of Health targeted to pregnant women and key populations. HIVST kits are distributed at the KCCA ANC clinics following health talks and sensitizations about the kit, the importance of male partner engagement, and assisted partner notification.

To align with this strategy, the study will also talk to women about HIVST and provide women with the option to take a kit home to her male partner, should they desire. HIVST kits are accompanied by written instructions in English and Luganda with pictures and diagrams that explain how to use them and provide a 24-hour phone number in case of reactive results, questions or help with the kit. HIVST will be offered during study visits, and also during ANC waiting room health discussions led by clinic staff, following MOH guidelines. We will follow good clinical practice guidelines to ensure that all people with a reactive result are supported and provided with confirmatory testing, treatment and care. Studies among pregnant women, men who have sex with men, and female sex workers have found that secondary distribution of HIVST kits can increase frequency of HIV testing among male partners and HIVST kits yield accurate results (43-45). In these studies, reports of partner-perpetrated violence were rare, indicating that people potentially used discretion when choosing partners to whom to offer HIVST (44). While HIVST is one strategy to increase HIV testing among male partners, there are still challenges associated with secondary distribution of these kits.

In the Obumu study, as of February 2020 we reached our enrollment target of 500 HIV positive pregnant women, and as of August 2020, 45% of male partners have been tested for HIV across both arms. We will remain blinded to male partner HIV testing rates by the arm that the woman was randomized to (i.e., secondary distribution of HIVST from pregnant HIV-positive pregnant women compared to the control arm of standard of care invitation letters from the clinic) until completion of Obumu follow-up in 2021.

Through the qualitative work in Obumu, we have learned that a number of women are hesitant to provide the kit to their partner, because they are not ready to disclose their HIV status and feel that their partner will only use the kit if they test together. A substantial number of women in the intervention arm expressed that they did not deliver the HIVST kit or invitation letter in the control arm due to her fears of the consequence of disclosure of her HIV status. As HIVST distribution is being rolled out on a national level, the use of HIVST will become more normalized and this strategy will be offered to women in both the control and intervention arms. However, evidence suggests that this strategy to get male partners tested for HIV may be more effective if integrated in conjunction with other services that men value (e.g., syphilis testing, blood pressure screening, visual acuity screening, and COVID-19 screening, and if available, COVID-19 PCR for those reporting possible COVID symptoms).

In our previous qualitative work, we found that men cite reluctance to attend healthcare facilities, which are thought to provide care mainly for women and children. Gender dynamics make it difficult for women to encourage their male partners to attend healthcare facilities. In focus group discussions, men stated that having a male counselor contact them to encourage linkage can help shift norms around clinic attendance while also taking the burden off female partners to motivate clinic attendance. In our ongoing Obumu trial, we found that men's linkage to care and prevention increased when we hired a male counselor to call men to encourage linkage. However, this intervention has not yet been systematically evaluated.

2) <u>Acceptability and convenience of wellness visits to increase male partner testing for HIV</u>

Momentum for the delivery of comprehensive preventative health services to men, who are typically isolated from preventative health care, is growing and can be leveraged to introduce HIV testing and linkage to HIV prevention or treatment. Men value health care services that do not interfere with paid work, or compromise confidentiality (46). By offering interventions that integrate HIV prevention with full-service preventative health care such as STI, hypertension, and blood pressure screenings, men may feel more motivated by the convenience.

To date, 46 male partners enrolled in the Obumu study have attended informal focus group discussions to provide their perspectives on opportunities to address the challenge of HIV testing and linkage to care. A vast majority of men in these focus group discussions have proposed integrating other public health services into a clinic visit, as the majority of the men are motivated to test for syphilis and feel that syphilis is less stigmatized and readily treatable compared to HIV. Through provision of HIV testing as part of a package of services offered through wellness visits, we may be able to increase the proportion of men who test for HIV at ANC clinics, and increase the proportion of men who link to HIV care or treatment. By linking HIV negative men to PrEP, an integrated PrEP as a bridge to ART strategy, can be used for serodiscordant couples in the study.

PrEP as an effective bridge to ART and viral suppression

We tested the effectiveness of an integrated PrEP and ART strategy in the Partners Demonstration Project among 1,013 ARV-naïve HIV serodiscordant couples at 4 sites in Uganda and Kenya, including IDI Kasangati in Kampala (NIMH R01 MH095507, Bill & Melinda Gates Foundation OPP1056051, USAID AID-OAA-A-12-00023) (47). 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% (48), who would most benefit from PrEP as a bridge to ART.

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 high uptake and adherence to ART among HIV-positive partners; 91% initiated ART by 24 months with >90% viral suppression (47). 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 (49). This integrated PrEP and ART strategy nearly eliminated HIV transmission with 95% reduction in HIV transmission (Figure 2) (47). High protection was observed among HIV-negative men (95% HIV reduction, p<0.0001), relevant to this project (50). We found PrEP until the HIV-positive partner initiated ART was highly acceptable, safe and effective (51). 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 (52, 53), Kenya (54), and Ugandan guidelines.

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

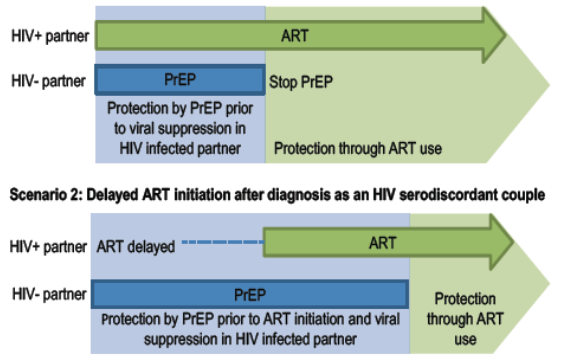
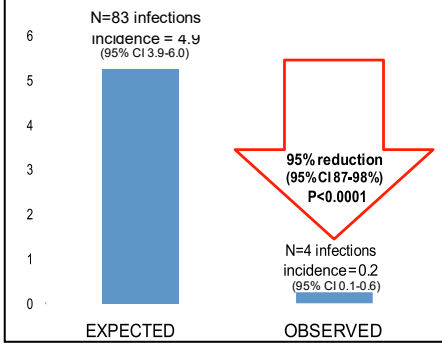


Figure 2. Observed vs expected HIV infections in the Partners Demonstration Project, with near elimination of HIV transmission.



The primary difference with the Obumu is that the HIV serodiscordant couples had already mutually disclosed in the Partners Demonstration Project. In Obumu and our proposed Obumu 2 project, we are evaluating interventions to address the challenges of lack of disclosure by HIV positive pregnant women which is one of the barriers in reaching male partners to test for HIV. We thus are evaluating innovative strategies to reach the male partners of HIV positive pregnant women so that the men can learn their HIV status and benefit from PrEP if HIV negative, as in the Partners Demonstration Project described above, or link

to ART if HIV positive.

Evaluation of interventions to support status disclosure to male partner and viral suppression among women living with HIV

Status disclosure

In PMTCT, status disclosure has been shown to significantly increase ART adherence and viral suppression (VS). In an observational study of 150 PWLHIV in southwestern Uganda with over 4 years of follow-up, women who disclosed to their partner were 4.5-fold more likely to achieve VS (82). Similar observations were made among 170 Nigerian PLWHIV; the most important motivator for ART adherence was desire to protect the infant; significant factors associated with VS were disclosure to their partner and having a treatment partner (83).

A systematic review of status disclosure by African PLWHIV reported factors associated with HIV disclosure for the woman (younger age, first pregnancies, knowing someone with HIV, lower levels of internalized stigma, lower levels of avoidant coping), partner (prior history of HIV testing, higher education), partnership (no history of domestic violence, financial independence), and household (higher quality housing, residing without spouses or extended family (84). A review of HIV status disclosure interventions in low and middle income countries found 4 studies among PLWHIV, most of which involved support groups with 4 to 10 sessions; the studies had mixed results on disclosure outcomes but were limited by small sample sizes and high attrition (85). A randomized trial of a problem-solving group intervention for depression and disclosure among Tanzanian PLWHIV showed that depression decreased and there was a trend towards increased HIV disclosure in the intervention arm (56% vs 46%; OR 1.2, p=0.19), but it was limited by 30% of women not being exposed to the intervention and high drop-out (86). There is a clear need for evidence-based and feasible disclosure support interventions for African PLWHIV.

Problem-solving therapy (PST) is an appealing approach for pregnant women facing psychological and behavioral challenges related to HIV status disclosure and motivation to continue ART post-partum because it aims to develop actionable solutions and improve coping around adherence issues (87). PST is recommended by the WHO for treating common mental health disorders in resource-limited settings given its flexibility, low cost, and lay counselor delivery. Core components include problem identification, generation of alternative solutions, decision-making, and solution implementation (88).

To address the challenges of status disclosure for PWLHIV in our previous study called Obumu, we piloted PST delivered through monthly peer support groups with a mix of women who had, and had not, disclosed their status to their partners. Peer support groups were facilitated by peer mothers (expert clients with HIV who have been trained in ART adherence counseling and hired by the Ugandan MoH)[46] and an Obumu staff member. Among the 157 PWLHIV enrolled in Obumu who participated in peer support groups (8-17 women per group), women reported that encouragement and suggestions from their peers motivated and helped them find ways to approach their partner about HIV testing and disclose their HIV status, providing preliminary data about the promise of this approach to support HIV status disclosure in this population.

In Kingasa, we will offer PST, delivered by trained peer mothers who participated in Obumu and have experience with status disclosure. Mothers will be selected and trained by nurse midwives who have expertise in PST and counseling about status disclosure from Obumu. Mothers who have enrolled in Kingasa will be offered problem-solving therapy one-on-one at antenatal visits as well as through group sessions. Acceptability and status disclosure pre- and post- problem solving therapy will be evaluated.

POC HIV Viral Load

Based on our preliminary analysis of women in Obumu who have had a 6 and/or 12-month post-partum visit, 24% and 34%, respectively, have not had a viral load recorded (compared to 98% at enrollment). Among postpartum who have had a viral load obtained, 20-22% had detectable viral load. Missing viral

loads and detectable viral load among postpartum women, combined with not receiving their results until their next postpartum visit indicates that a substantial proportion of postpartum women living with HIV are not receiving the benefit of viral load monitoring and prompt ART adherence counseling. Additionally, DNA-PCR coverage for early infant diagnosis (EID) in Uganda is suboptimal; only 64% of HIV exposed infants (HEI) received an initial DNA PCR test delivery, < 55% of HEI receive a virological test within 2 months of birth, and only 28% receive their final rapid test at 18 months of age (89).

The feasibility of POC VL with Xpert HIV-1 VL at the time of delivery combined with neonatal diagnosis EID using the Xpert HIV-1 EID has been demonstrated in South Africa (90). Approximately 75% of mothers and newborns received the maternal POC VL and EID prior to discharge (91). A field evaluation of POC EID for neonatal diagnosis in South Africa showed good performance, improved rates of results returned to mothers (96% compared to 89% of lab-based EID), and reduced time to ART initiation for infected neonates (5 days earlier for infants diagnosed with the Xpert HIV-1 EID). Additional evaluation is needed in non-tertiary obstetric units and health centers in terms of feasibility of introducing POC maternal VL and EID in terms of implementation aspects, coverage, turn-around time, and results return before women are discharged after delivery.

Our co-investigator, Dr. Paul Drain, demonstrated in the STREAM study among 390 PLWHIV in KwaZulu-Natal South Africa, that POC VL using the Cepheid Xpert HIV-1 viral load assay with same day adherence counseling by nurses (i.e., task shifting) was associated with a 13.9% increase in viral suppression and retention in care compared to the control group, which received VL results and counseling at their next visit.(26) There were no adverse events, both patients and providers preferred POC testing over lab-based testing, and POC VL testing was cost-effective compared to laboratory-based VL testing, which requiring 2-3 weeks turnaround.(27) POC VL testing enables real-time targeted ART adherence counseling but has not been evaluated among pregnant and postpartum women, for whom viral suppression is important not only for their own health, but also to reduce the likelihood of vertical HIV transmission.

In the Kingasa study, women randomized to have POC VL at enrollment, delivery and 6 months post-partum, will have a finger prick to obtain whole blood for the Cepheid Xpert HIV-1 RNA cartridge on the Xpert IV machine with results in 90 minutes. Women who are randomized to POC VL who have VL >200 c/ml will receive additional adherence counseling, following the STREAM protocol, [26] to address the challenges that they are having with ART use. At the delivery visit, infants of women in the POC VL arm will also have viral load testing done.

Summary

It is critical to evaluate strategies to leverage women's engagement in antenatal care to increase male partner testing. Secondary distribution of invitation letters for wellness visits from pregnant women to their male partners could be an innovative strategy to overcome barriers to men's reluctance to come to antenatal clinics for HIV testing. If men are motivated to attend ANC clinic's that offer a package of preventative health services, then the uptake and acceptability of testing for HIV at the clinic may improve as well. Increased proportions of men who test for HIV can then improve the number of men who link to HIV prevention and care services. For pregnant and postpartum women with HIV, partner testing and disclosure could facilitate women's continuation of ART post-partum. Thus, multiple public health goals could be achieved through increasing the proportion of men who know their HIV status.

STUDY METHODS

Overall design

This is a randomized factorial trial to assess two strategies; one to increase HIV testing and engagement

in care among male partners of pregnant women, and the second to improving ART continuation and adherence among the HIV-positive pregnant women. The overall goal is to evaluate the impact of innovative strategies to increase male partner HIV testing, and engagement in HIV care and prevention among men and their pregnant partners, through ANC services provided to HIV- positive women.

We will recruit HIV-positive women with a partner of unknown HIV status through PMTCT B+ programs at Kitebi Health Center III in Kampala. Women will be randomized 1:1:1:1 to

Arm 1: Women will be provided the standard of care invitation letter for male partners for fast-track visit for HIV testing and laboratory HIV testing at enrollment and every 6 months until 6 months postpartum,
Arm 2: Women will be provided the standard of care invitation letter for male partners for fast-track visit for HIV testing and POC VL tests for women at enrollment, delivery, and 6 months post-partum;
Arm 3: Women will be provided an invitation letter for male partners for wellness visits and laboratory-based HIV VL testing for women at enrollment, delivery, and 6 months post-partum;
Arm 4: Women will be provided an invitation letter for male partners invitation letter for male partners for wellness visits and POC viral load testing for women at enrollment, delivery, and 6 months post-partum.

Women who are randomized to receive POC VL will receive same day ART adherence counseling and those randomized to receive lab based VL will receive VL results at their next visit with ART adherence counseling based on their VL results.

Male partners of women who are randomized to the wellness visit will receive a phone call from a male counselor after HIV testing to encourage linkage to care and prevention, depending on HIV status.

We will encourage men who test HIV-negative to use PrEP until their partner has achieved viral suppression (typically six months). However, all HIV-negative men will be offered PrEP, and men who test HIV- positive will be encouraged to start ART. Per recent Ugandan MOH guidelines, women in both arms will be provided HIVST kits for their partners with self-instruction materials about HIVST, encouragement to seek confirmatory testing and counseling, and brief educational materials about PrEP and ART, along with instruction in the use and interpretation of HIVST.

All women and men in the cohort will be screened for COVID-19 symptoms.

The primary endpoint of the randomized intervention for male partners is the proportion of male partners who test for HIV at the clinic, during the study. The primary analysis is an intent to treat comparison by randomization arms (comparing Arms 1 and 2 combined to Arms 3 and 4 combined) of the proportion achieving the primary outcome. The secondary outcome is engagement in care of the male partners, defined as 1) for HIV-negative men initiating PrEP within six months of randomization of their HIV-positive partner is randomized, and 2) for HIV-positive men, initiation of ART within 6 months after their HIV positive partner is randomized. Quantitative and qualitative methods will be used to assess acceptability of dual syphilis and HIV testing, blood pressure, visual acuity screening, and COVID-19 screening as part of wellness visits for male partners whose partner was randomized to the intervention arm, PrEP among male partners who test HIV negative, ART among male partners who test HIV positive, and identify ways to minimize social harms through antenatal programs that try to reach men.

The primary endpoint of the randomized intervention for pregnant women with HIV is viral suppression at 6 months post-partum. The primary analysis is an intent to treat comparison by randomization arm (arms 1 and 3 combined compared to arms 2 and 4 combined) of the primary outcome, of the proportion of women living with HIV who are virally suppressed at 6 months post-partum by arm, as the measure of continuation of ART and high adherence post-partum.

Objectives

Aim 1: To determine the proportion of male partners of pregnant HIV-positive women who test for HIV at the clinic, based on invitation to a wellness visit (dual syphilis and HIV rapid test, blood pressure, visual acuity screening and COVID symptom screening, and if available, PCR testing for those with symptoms) compared to the standard of care (standard of care invitation letter for HIV fast track testing at the clinic).

Innovations are needed to address the challenges associated with male partner engagement during their partner's antenatal and postpartum care periods. Provision of wellness visits providing STI testing and general health services, may overcome male partners reluctance to be tested in PMTCT clinics. We will randomize women 1:1 to the intervention and control arm and determine the proportion of male partners who test for HIV based on male enrollment numbers and data on HIV testing.

Primary outcome: The proportion of male partners who test for HIV compared by arms (comparing Arms 1 and 2 combined to Arms 3 and 4 combined).

Aim 2: To evaluate whether POC viral load testing with same day ART adherence counseling improves ART continuation, and viral suppression among pregnant women living with HIV.

Point-of-care viral load (POC VL) testing has been demonstrated to enable task-shifting and real-time adherence counseling.26 It is innovative to utilize POC VL for pregnant and post-partum women for real-time assessment of ART adherence, to improve ART use, retention in care, and viral suppression post-partum.

We will assess POC viral load monitoring and targeted ART adherence counseling compared to the standard of care laboratory-based HIV RNA testing, (comparing arms 1 and 3 combined to Arms 2 and 4 combined). Primary outcomes are viral suppression and HIV status disclosure at 6 months post-partum. *Hypotheses*: *POC viral load testing and same day adherence counseling will increase ART continuation and viral suppression*

Primary outcome: The proportion of HIV-positive women who are virally suppressed at 6 months post-partum. Viral suppression will be defined as plasma viral load <50 copies/ml.

Aim 3: To evaluate whether engagement in care is improved among male partners who are provided a phone call follow up from a male counselor after HIV testing compared to standard of care.

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 linkage to HIV treatment or care among all men enrolled in the study.

Engagement in care is defined as initiating PrEP for men who test HIV-negative and initiating ART for men who test HIV-positive, both within 6 months of their partner's randomization. Men who do not test are defined as not engaged in care.

Primary outcome: Proportion of HIV-negative male partners who initiate PrEP and HIV-positive men who initiate ART within 6 months across both arms. The secondary outcome will evaluate the proportions who initiate PrEP and ART by arm.

Aim 4: To evaluate acceptability and preferences for HIV testing and other health services among men using qualitative methods.

We will use quantitative and qualitative methods to assess acceptability and preferences for dual syphilis and HIV testing, blood pressure, visual acuity screening and COVID-19 testing among men attending wellness visits. We will assess acceptability and preferences of strategies to improve male partner testing, among female participants. Quantitative behavioral data will be collected from the study cohort during clinic visits using multiple validated questionnaires. Focus group discussions or in-depth interviews will be held with men who volunteer to join. These discussions will aim to achieve a better understanding of barriers and to motivators to seeking HIV care, testing for HIV, and acceptability of wellness visits.

Population

Two hundred HIV-positive pregnant women ≥18 years of age, or if aged 14-17 are qualified as emancipated minors, with male partners of unknown status, will be recruited from PMTCT B+ programs in Kampala.

Eligibility

For women

- Age ≥18 or 14-17 years if an emancipated minor (pregnant or have a child)
- Currently pregnant
- 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
- Able and willing to provide written informed consent
- Able and willing to provide adequate locator information for study retention purposes
- Screening negative for any indication of intimate partner violence or social harm

Sample size

A total of 200 pregnant women living with HIV and their male partners.

Recruitment

IDI Kasangati has long-established recruitment and retention strategies to identify and enroll 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, safety and efficacy of PrEP, 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. IDI Kasangati will work directly with the Kitebi KCCA facility, including antenatal care/PMTCT programs, to identify pregnant HIV-positive women attending PMTCT B+ services. Health care workers and study staff at Kitebi ANC clinic will provide general information sessions to inform potential participants.

Study Enrollment

Women will be enrolled and followed at the Kitebi ANC clinic. Trained research staff will counsel potentially eligible women about the benefits of male partner testing, post-partum ART persistence for HIV-positive women, PrEP safety and effectiveness for HIV-negative persons, and possible participation in the study. Counseling messages will include:

<u>Reasons for male partners to be tested for HIV</u>:

- To know his status.
- If he is positive that he does not 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 and have screened negative for recent or potential social harms will be asked to provide informed consent for study enrollment. Women will be asked if they would like a male study staff member to contact their partner directly by phone to encourage him to come to the clinic, per standard of care guidelines. Partners who come to clinic for a wellness visit or come for HIV testing in response to an invitation letter will be offered the opportunity to consent for study enrollment. Men will consent to participate in the study and receive open label PrEP or ART, depending on HV status. Participants will be asked 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 an invitation letter with infographics about the components of a wellness visit or an invitation letter for fast-track HIV testing to provide their partner.

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 6 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 Table 1.

Figure 3: Factorial Design of Study Groups

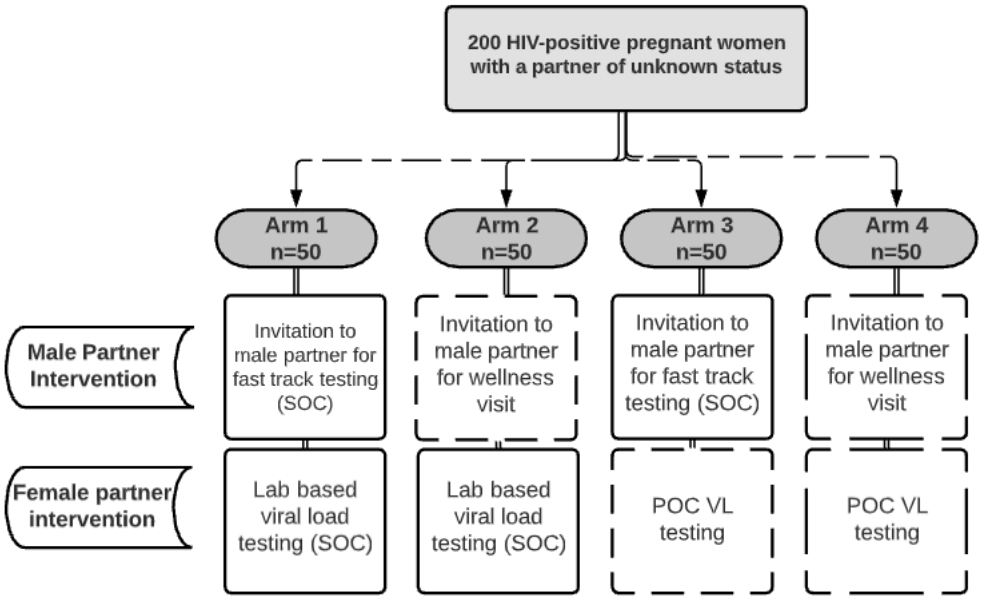


Table 1: Factorial design for study arms 2 x 2 factorial design (4 arms)		**Male Partner wellness visit**	
		Control	Intervention
POC HIV viral load testing	Control	Arm 1: SOC invitation letter for male partner and laboratory HIV testing for female (SOC) (N=50)	Arm 2: invitation to male partner for wellness visit, laboratory HIV testing for female (SOC) (n=50)
	Intervention	Arm 3: Invitation to male partner for fast-track testing (SOC) and POC VL testing for female (n=50)	Arm 4: POC VL for female + invitation to wellness visit (N=50)

HIV-positive pregnant women will receive a 3-month supply of ART refills at the Kitebi or Kasangati antenatal clinic sites through the Infectious Diseases Institute (IDI) ART program. Women who are screened for this new cohort, called Kingasa (Luganda for 'It benefits me'), will be screened for COVID-19 symptoms. HIV-positive pregnant women who are screened for Kingasa will also be screened for GBV and those with recent GBV will be offered referrals for GBV services. Women who consent to participate will be randomized to receive at the Kitebi ANC:

a) POC VL and same day ART adherence at enrollment, delivery, and 6 months postpartum (Arms 1 and 3)
b) SOC laboratory-based HIV RNA testing and adherence counseling at their next visit (Arms 2 and 4; Figure 3 and Table 1).

Randomization with a factorial design is the most efficient for evaluating efficacy of POC VL with adherence counseling and a wellness visit to increase male partner testing for HIV, assuming that the interventions operate independently. This is a reasonable assumption since the two interventions affect different person in the couple with separately ascertained outcomes: VL is a direct measure of ART adherence with very brief counseling by the nurse counselor focused on ART adherence in the HIV-positive women whereas HIV testing and engagement in care are assessed at clinic visits for the male partner.

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.

Women will be randomized to provide their male partner with either an invitation to a wellness visit

(intervention) or invitation for fast-track HIV testing (standard of care, SOC)

Pregnant women will be randomized to give their male partners either an invitation letters for a wellness visit (Arms 3 and 4) or an invitation letter for fast-track HIV testing to give to their male partners ((Arms 1 and 2). The objective of this intervention is to evaluate the implementation and outcomes of invitation letters offering dual syphilis and HIV testing, blood pressure and visual acuity as part of a wellness visit, compared letters for fast-track HIV testing in the antenatal clinic (SOC).

Invitation of male partners to wellness visit (intervention group)

Pregnant women in the intervention group will be provided an invitation letter to give to their partner detailing information on services provided during a wellness visits at the ANC. Services will include dual syphilis and HIV testing and treatment, hypertension screening, a vision exam, and COVID-19 symptom screening. The wellness letter will include infographics to depict these services in an engaging way and appeal to men who have low levels of literacy or are illiterate. These invitation letters will be pre-tested on men, including those enrolled in the Obumu study, to elicit feedback on content and layout.

Invitation of male partners for fast-track HIV testing (standard of care group)

Women in the control arm will be provided letters to deliver to their partner to invite them to come for HIV testing to the ANC clinic for fast-track testing at Kitebi, alone or as a couple (standard of care). Fast track testing will allow men to show to up to the clinic with their invitation card and receive HIV testing and counseling without having to go through the normal clinic flow, thus minimizing time at the facility. Similar to the intervention group, invitation letters 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.

HIVST kits

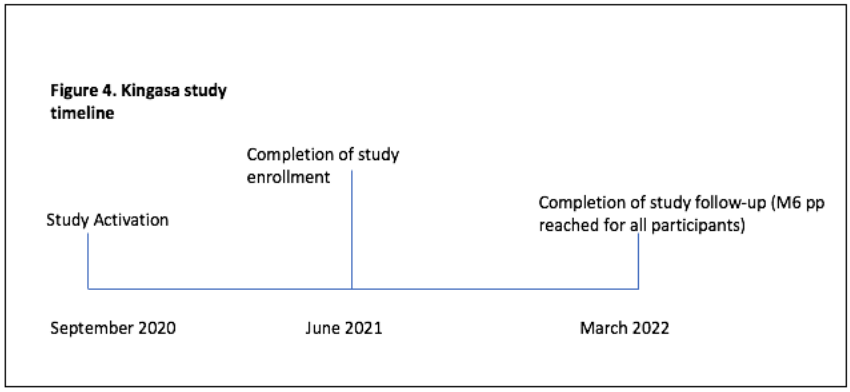
Following current MOH guidelines for secondary distribution of HIVST in ANC clinics, all women will be given one or two HIVST kits to bring home to their partner. They will be provided a brief demonstration of how to use the self-test and will be given two oral fluid based HIV self-tests (Oraquick rapid 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 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 not obligated to encourage their partner 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 messaging with women, 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.

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 (64). Pregnant women will have up to 4 antenatal visits before delivery with 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. Women randomized to the POC VL arm will receive POC VL testing at her delivery, as well as POC EID testing for her infant. After delivery, women will be followed quarterly for up to 6 months. Women in both arms will be screened for COVID-19 symptoms, and those with symptoms will be tested by SARS-CoV-2 PCR and those without symptoms will be screened for antibodies. Those who are PCR positive will be referred to a medical officer for clinical evaluation and contact tracing.

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 POC VL testing at enrollment, delivery, and every 6 months until M6 post-partum for women randomized to the intervention arm, and laboratory HIV RNA testing at enrollment, and every 6 months until M6 post-partum for women randomized to the control arm. Blood samples will be batch-tested at collaborating laboratories. 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 scheduled for week 6, and months 3 and 6. During these clinic visits, women will complete interviewer-administered surveys to collect data on behavioral factors that could mediate women's post-partum ART use. Women in the intervention arm will be provided their viral load results at that visit, and in the control arm will receive their viral load results at their next visit, in addition to counseling about the relationship between adherence, viral load and transmission risk.



Management of Viral Load Results

Participants in the intervention arm will have all routine ART monitoring tests performed according to the schedule described in the SoC arm follow-up procedures, however the POC VL assays will be utilized instead of lab based VL testing. POC VL testing will be performed using Cepheid's GeneXpert® HIV-1 VL assay performed at the beginning of the clinical encounter, so the clinical examination can be performed during the 90 minutes required to run a GeneXpert HIV VL test. If the participant is not able to wait for the results, then the study team will allow the participant to leave the study clinic but will ask them to remain in the vicinity and return to the clinic for their VL results. Prior to consent and enrollment, all potential participants will be counseled on the study procedures to ensure participants are able to comply with Intervention Arm study procedures, including potentially spending more time in clinic to receive VL results than they normally would as part of SoC clinic procedures. The GeneXpert testing will be conducted in the adjacent clinic site laboratory. Results will be managed according to SoC South African guidelines.

The clinical decisions from the SOC VL testing will adhere to the Ugandan guidelines. The algorithm for the current VL monitoring guidelines is summarized below:

- HIV VL <50 copies/mL: Reinforce the importance of good ART adherence and continue routine VL monitoring
- HIV VL 50-999 copies/mL: Provide standard of care ART adherence counseling, provide ART,

and ask participant to return to the clinic in six months for repeat VL testing. If the VL remains high (50-999 copies/mL) upon repeat testing, then the participant should continue receiving enhanced adherence counseling and repeat VL testing every six months until viral suppression (<50 copies/mL) is achieved.

- HIV VL ≥1,000 copies/mL: Provide standard of care ART adherence counseling; provide ART and ask participant to return to the clinic in three months for repeat VL testing. If the VL remains high (≥1,000 copies/mL) after repeat testing, then participants will be considered for switching to second line treatment according to Uganda guidelines.

Male partner procedures

Male partners of women enrolled in the study will be recruited using established recruitment methods during the initial Obumu study. These strategies operationalize protocol-specified requirements and ensure participant privacy for eligibility determination. Men will be referred to Kitebi clinic, either through invitation letters for wellness visits or standard of care clinic visits (Fig 4). Wellness visits will include provision of the following: a dual HIV and syphilis rapid test, eye exams, blood pressure checks and COVID-19 screening (and if available, COVID-19 PCR those with symptoms or antibody testing for those without symptoms). Those who are PCR positive will be referred to a medical officer for clinical evaluation and contact tracing. Men in both arms 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. Obumu male staff members will also contact male partners of women in the intervention arm of the study if their female partner gives permission. 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 6 months will be offered an opportunity to undergo study screening. Men will have up to 6 months to enroll in the study after their female partner enrolls.

Standard of care counseling about PrEP and ART

Participants will receive behavioral counseling on the effectiveness of ART and PrEP for men depending on their test results, and ART benefits and need for adherence during pregnancy as well as post-partum ART for the pregnant HIV positive woman. 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. 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 2. Components of HIV prevention delivery for HIV serodiscordant couples in 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, 3 and 6 months post partum)
PrEP counseling & provision	HIV-negative men: counseling about PrEP benefits & adherence (enrollment, quarterly visits at months 3 and 6)
6-monthly CD4 testing	HIV-negative men: assessment of acute HIV infection, PrEP provision HIV-positive women: HIV RNA testing (6 months post-partum)
Annual HIV RNA testing,	HIV negative men who initiate PrEP: baseline and 6-monthly renal function monitoring, urine for tenofovir testing at 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 couple 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 2).

PrEP medication and dispensation

PrEP will be offered to HIV-negative men according to national guidelines (47), 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, and they test HIV negative on rapid HIV tests. PrEP will be dispensed in a 3-monthly supply. HIV testing will be conducted at months 3 and 6 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 at baseline and 6-months for men who initiate PrEP.

The study will provide open-label PrEP to HIV-negative male partners for 6 months or until their HIV-positive 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 IDI Kasangati, abstracted in real time from pharmacy records and entered into an electronic database. Adherence will also be assessed through urine tenofovir drug levels in male partners 3 and 6 months after PrEP initiation. These point of care kits provide an inexpensive and accurate alternative to plasma or DBS to quantitively measure adherence.

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 (65).

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 IDI Kasangati– 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 (66). Men who are tested through HIVST will receive confirmatory testing, either at the ANC where their partner receives care or at IDI Kasangati. 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 at a clinic of their convenience or at IDI Kasangati. The recommended first line regimen in Uganda is tenofovir-lamuvidine-dolutegravir. 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. POC VL monitoring will occur at the Kingasa enrollment visit, delivery and at the 6 month postpartum visit. POC VL results will be used to support same day adherence counseling.

Table 3. 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 (47, 67)
Sexual behavior with study partner and other partners	Tool piloted in multiple couples-based HIV prevention services (47, 68)
Internalized stigma	Internalized AIDS-related stigma scale (69)
Fertility desires	Tool piloted in multiple couples-based HIV prevention services (47, 68)
Relationship power	Sexual Relationship Power Scale (70)
Intimate partner violence	Conflict Tactics Scale (71, 72)
Alcohol use	Rapid Alcohol Screen (71)
Self-efficacy of ART use	HIV Medication Self-Efficacy Scale (73)
Social support	Social Support Questionnaire- Short Form (74)
Symptoms of common mental disorders	Self Reporting Questionnaire 20-item (75)
Depressive symptoms	Patient Health Questionnaire 2-item (75)
HIV-negative men	
HIV prevention preferences among men (Aim 1)	Tool piloted in multiple couples-based HV prevention studies (47, 68)
Self-perceived risk of HIV	Tool piloted in multiple couples-based HIV prevention services (47, 68)
Sexual behavior with study partner and other partners	Tool piloted in multiple couples-based HIV prevention services (47, 68)
HIV-positive men	
Sexual behavior with study partner and other partners	Tool piloted in multiple couples-based HIV prevention services (47, 68)

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 experience providing the intervention arm letter or control arm letter, as well as their partner's testing and outcome at their PMTCT visits. Women in the intervention and control groups whose partners do not come for testing, 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, social support, and symptoms of common mental disorders (Table 3).

HIV seroconversion

Study staff will counsel male partners who seroconvert 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, POC plasma VL testing and CD4 after HIV seroconversion.

Final study visit

Women will be followed for 6 months post-partum and male partners will be followed for 6 months after enrollment into the study. At this time, 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 PrEP where available through demonstration projects or the public health system.

Quantitative surveys

A structured interview administered to all HIV-positive female partners at enrollment will ask about knowledge of the partner's HIV status, disclosure, fertility desires, relationship power, intimate partner violence, social support, and symptoms of common mental disorders. 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 the acceptability of delivering a letter for a wellness visit to their partners and administered to men about the acceptability of wellness visits that integrate HIV testing and linkage to care.

Data quality and management

Health information about the mother and child during pregnancy, delivery and after delivery will be documented. Clinic and pharmacy records will be used to document PrEP prescriptions, 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

The goal of the qualitative component is to assess the acceptability of community-based ART refills, POC VL and targeted adherence counseling to pregnant women in PMTCT B+ and the wellness visits for 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. This broader scope allows for addressing "how" and "why" questions about intervention dynamics to inform future dissemination and implementation.

Qualitative data collection will consist of 1) in-depth interviews (IDIs) with men and women in the qualitative sample, and 2) field observations of intervention activities.

Individual In-depth Interviews

A purposeful sample of 15 women participants receiving POC viral load testing and 15 male partner

participants receiving invitation letters for wellness visits will be identified for the qualitative IDIs (Total: 30 interviews with participants). Variation in age and socioeconomic characteristics will be represented as part of purposeful sampling

IDIs will explore experiences of intervention components from the perspective of individual participants. Examples of questions for women participants receiving intervention components might be what kinds of difficulties they encountered with transport, unintended disclosure or stigma? Examples of questions to be addressed with male partner participants are: 1) How did the wellness visit compare with experiences in clinic? 2) How did the receipt of preventive services during wellness visits impact the decision to test for HIV, if at all? IDIs will be carried out by trained Ugandan research assistants and will be conducted in private locations at clinics or in the community. They will take place in the interviewee's language of choice (Luganda, English) and will be audio-recorded, with permission, and transcribed.

Field Observations

We will conduct 10 field observations of intervention activities, such as the wellness visits and the conduct of viral load testing. Observations will be conducted by trained RAs and recorded as field notes on a structured template that organizes narrative descriptions by topic.

Qualitative data analysis

The goal of the qualitative analysis is to produce an in-depth analysis of acceptability of intervention components from the points of view of male and female participants. The construct of acceptability is broadly defined to target not only participants' feelings and attitudes toward the intervention, but also allow for the interpretation of their broader experiences with intervention components. The qualitative analysis will address "how" and "why" questions about intervention dynamics to inform future dissemination and implementation.

All qualitative data will be analyzed using an inductive content analysis approach. First, we will review the data to derive a general sense of content relevant to the construct of acceptability. Following the initial review, a subset of the data will be re-reviewed to descriptively label relevant sections of text (open-coding). Descriptive labels will be defined, illustrated, and assembled into a codebook to guide directed coding, in which the codebook is used to code the entire data set. The directly coded data will be iteratively grouped and regrouped to identify relevant emergent content. Results will be rendered as conceptual categories consisting of labels, descriptive text, and illustrative quotes, and linked through grounded interpretation.

Sample size considerations

Aim 1: The primary analysis will be an intent to treat comparison by randomization arms of the primary outcome of the proportion of women whose male partners who test for HIV, comparing Arm 1 and 2 combined to Arms 3 and 4 combined.

Aim 2: The primary analysis will assess proportion of women who are virally suppressed at 6 month post-partum by randomization arms comparing Arm 1 and 3 combined to Arms 2 and 4 combined.

Power to detect a difference in HIV testing uptake in male partners with 200 women

Power is 80% to detect an increase in HIV testing of 20-22% in the male partner testing, as shown in Table 4, assuming:

- the test uptake in the standard of care arm is 20-30% (20% observed in MU-JHU's program and anticipating some increase with new MOH program to offer HIVST in ANC programs)
- test uptake in intervention arm is 42-50% (assuming that the broader services offered in the intervention arm through wellness visits will increase HIV testing by 20-22%)
- Power is based on a log-rank test for time from randomization of a pregnant woman to her male partner receiving HIV test in the clinic

Power to detect a difference is viral suppression in female partners with 200 women

Assuming 60-80% of pregnant women in Kingasa will be virally suppressed at 6 months post-partum in the standard of care arm (which is lower than Obumu due to the impact of COVID-19 on women's ability to leave home for ART refills and adherence among women who have not disclosed), we have 80% power with a two-sided alpha of 0.05 to detect an 13-18% increase in viral suppression as a result of the POC VL test (Table 4).The primary analysis for effectiveness of male testing will compare Arms 1 and 2 combined compared to Arms 3 and 4 combined, the primary analysis for effectiveness of POC VL and targeted adherence will compare the two groups with and without POC VL (i.e. Arms 1 and 3 combined compared to Arms 2 and 4 combined). An intention to treat approach will be used.

Table 4: Statistical power to detect a difference in male partner HIV testing (Aim 1) and Viral suppression in the HIV-positive female partner (Aim 2)

Aim 1:	Probability of outcome in SOC conditions	Outcome change that can be detected with 80% power	**Aim 2:**	Probability of outcome in SOC conditions	Outcome change that can be detected with 80% power
Outcome: Male Partner tested for HIV (N = 200)	20%	22%	Outcome: VS of the women at 6 months post-partum	60%	18%
	25%	21%		70%	16%
	30%	20%		80%	13%

The analysis for HIV testing in the male partner will use Kaplan Meier methods to estimate the proportion of women who have their male partner tested during the study, using time from the women's enrollment until her partner tests. The proportion will be assessed at 6 and 12 months as the survival curve estimate at the end of the visit window. A log-rank test will be used to evaluate the difference between arms in proportion tested. The analysis for VS at 6 months post-partum will use logistic regression to assess the odds of VS at the 6-month post-partum visit.

Outcome measurements

Aim 1: The outcome for Aim 1 is the proportion of men who come to the ANC clinic to test for HIV in the intervention arm compared to those randomized to the control arm, including whether they initially used a HIVST before coming to the clinic.

Aim 2: The outcome for Aim 2 is viral suppression at 6 months postpartum, assessed at this visit.

Aim 3: The primary outcome is the proportion of HIV-negative male partners who initiate PrEP and HIV-positive men who initiate ART within 6 months across both arms. The secondary outcome will evaluate the proportions who initiate PrEP and ART by arm. The outcomes are engagement in care, defied as: 1) PrEP initiation among HIV negative men or 2) ART initiation among HIV positive men. PrEP use will be measured by pharmacy records where men are dispensed PrEP (e.g.at Kitebi clinic or IDI Kasangati), and self-report through a validated questionnaire. ART initiation will be assessed through pharmacy records.

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, 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.

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 Diseases 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 Diseases 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 enrollment. Participants will be offered copies of the informed consent forms. The study site will draft informed consent forms that describe the purpose 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.

ART adherence counseling. Participants may become embarrassed, worried, or anxious when talking about their emotions and/or experiences. The counseling staff, including peer mothers, will be highly trained to protect participant's confidentiality and privacy while minimizing uncomfortable feelings. Participants may also experience more intense psychological discomfort during counseling sessions or data collection due to disclosure about common mental disorders or fears of intimate partner violence. Steps will be taken to minimize any psychological discomfort by providing ongoing counseling during study visits and access to staff by WhatsApp and telephone, as needed. Lists of referrals are in place to address recent psychological problems needing intervention. Participants who disclose suicidal ideation, or a history of suicide attempt, either through their questionnaire responses or in conversations with study staff, will be immediately linked to further medical care.

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 [a RRR] 0.10; 95% CI: 0.02-0.47) or couple testing (a RRR 0.13; 95% CI: 0.03-0.54) (76). 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 (a OR 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-positive women and in 2.2% of visits by HIV-negative women (77). In the Partners PrEP Study, HIV-negative women in serodiscordant partnerships reported IPV at 0.7% of study visits (78). 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 positive partners on ART, and this mutual reinforcement motivates couples who wish to stay together to do so (79).

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 (80). 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 (38). 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 (81).

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 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.

Informal Focus Group Discussions. The risks of participating in the informal focus group discussions are minimal, and participation is voluntary. It is possible that participants might become tired during the focus group. They may also find some of the questions uncomfortable or hard to answer. Participants can choose to leave the focus group discussion at any point.

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, 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.

Women in the study 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. Men in the intervention arm will be provided with additional health services as part of the wellness visit.

Care for HIV-positive male partners

This study will identify male partners who are HIV-positive, 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 positive 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 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
Mildmay Uganda Research Ethics Committee
The Uganda National Council for Science and Technology
The Uganda National Drug Authority

Table 5. Procedures for HIV-positive pregnant women

	ANTENATAL				Delivery	POSTNATAL	
	T1	**T2**	**T3**	**T4**		**M3**	**M6**
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
Collect/update demographic information	[X]	[X]	[X]	[X]			
Obtain random allocation	[X]	[X]	[X]	[X]			
Schedule next visit	[X]	[X]	[X]	[X]		X	X
COUNSELING							
HIV/STI risk reduction counseling, condom provision	[X]	[X]	[X]	[X]		X	X
Standard of care counseling (ART adherence, clinical & prevention benefits)	[X]	[X]	[X]	[X]		X	X
CLINICAL PROCEDURES							
Provide HIV test results	[X]	[X]	[X]	[X]			
Medical history	[X]	[X]	[X]	[X]		X	X
Perform physical exam	[X]	[X]	[X]	[X]		[X]	[X]
STI syndromic assessment and management	[X]	[X]	[X]	[X]		[X]	[X]
Referral for / provision of ART according to national guidelines	[X]	[X]	[X]	[X]		X	X
PMTCT PROCEDURES*							
Antenatal care package	[X]	[X]	[X]	[X]			
Postnatal care package						[X]	[X]
Infant HIV status at 6 weeks						X	
LABORATORY PROCEDURES							
Syphilis testing	X	[X]	[X]	[X]			
HIV serology	X	[X]	[X]	[X]			
Plasma HIV viral load (control arm)	[X]	[X]	[X]	[X]			X*
POC viral load (intervention arm) with same day ART adherence counseling	[X]	[X]	[X]	[X]	X		X

*Standard of care
Study staff will perform study specific procedures at collaborating clinics

LEGEND
[ ] as indicated
T = trimester

* Point of care (POC) viral load with same day adherence counseling in the intervention arm and laboratory-based HIV VL and adherence counseling at the next visit in the control arm

Table 6. Procedures for male partners

[ ] as indicated
*Three months after study enrollment

	E	M3*	M6
ADMINISTRATIVE AND REGULATORY PROCEDURES			
Obtain written informed consent	X		
CLINIC PROCEDURES			
Provide HIV test results and post-test counseling	X		
Medical history	X		
Perform physical exam	X	[X]	[X]
STI syndromic assessment and management	X	[X]	[X]
Dual syphilis-HIV rapid test (intervention arm only)	X	X	X
Blood pressure screening (intervention arm only)	X	X	X
Visual acuity screening (intervention arm only)	X	X	X
COVID-19 screening and if available, testing (intervention arm only)	X	X	X
Syphilis testing (control arm)	X	X	X
HIV-NEGATIVE MEN			
Provide HIV test results		X	X
Hepatitis B surface antigen	X		
Creatinine	X		[X]
PrEP provision	X	X	X
HIV-POSITIVE MEN			
Referral for / provision of ART according to national guidelines	X	X	X
Assess ART use and linkage/retention in care		X	X
POC HIV viral load with same day ART adherence counseling*	X		X

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
POC HIV plasma viral load with ART linkage and adherence counseling	X	X	X	X
HIV serology (confirmatory EIA)	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

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