Brief Title: Male Partner Engagement in HIV Testing Using Partner-notification Slip Plus Oral HIV Self-testing Kit

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Title: Assessing male partner engagement in HIV testing using partner-notification slip plus oral HIV self-testing kit among male partners of HIV-negative pregnant women

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Abstract

In Malawi, and other sub-Saharan Africa (SSA) countries with high HIV burden, HIV testing uptake among men is lower compared to women. New interventions are being sought to encourage men to go for HIV testing. Through this study, we will assess if giving a notification slip plus HIV Self-testing kit to HIV-negative pregnant women with syphilis attending antenatal care can increase the number of men reporting for HIV testing compared to giving the women a notification slip only (standard of care). The objectives of this protocol are: (1) Compare the acceptability of male partners' engagement in HIV testing using partner-notification slip plus oral HIV Self-test to partner-notification slip only among male partners of HIV-negative pregnant women with syphilis; (2) Identify demographic and sexual behavior factors associated with male partners' return to clinic for HIV counselling and testing; and (3) Evaluate if using partner-notification slip plus HIV self-testing among HIV-uninfected pregnant women is associated with any social harm. Results are expected to inform if HIV self-testing for partners of HIV-negative pregnant women with syphilis can be incorporated in antenatal care.

Background and Justification

Despite the increasing campaign for HIV testing in sub-Saharan Africa, HIV testing uptake among men remains lower than among women. The tendency of men not to seek HIV testing and counseling (HTC)[1-5] has resulted in poor outcomes along the HIV-care cascade such as low rate of ART initiation[6-9] and poor retention in care.[10] It is therefore important that new strategies to encourage men seek HIV testing are developed and implemented.

Similarly, male partner engagement in Malawi's antenatal care (ANC) program remains poor[11,12] although male partner engagement in antenatal care-seeking of their HIV-infected female sexual partners is associated with marked improvements in maternal and infant outcomes.[12-14] As a standard of care in Malawi, all pregnant women attending ANC are tested for HIV and syphilis (pregnant women with syphilis run the risk of severe fetal anomalies and miscarriages). Pregnant women who test positive for HIV are encouraged to bring their partners for HIV counselling and testing. If the pregnant woman is diagnosed with syphilis, she is given partner-notification slip inviting their male sexual partners to come to clinic for syphilis testing and treatment services.

HIV self-testing (HIVST) is an emerging approach to HIV testing. HIVST is a process in which individuals collect their own specimen, perform the test and interpret the results.[1] If reactive, the results need to be confirmed through additional testing by a trained provider. HIVST was highly acceptable to men in Malawi.[15,16] If well implemented in ANC, HIVST has the potential to increase male engagement in HIV counselling and testing.[17]

However, partner-notification slip plus oral HIVST for sexual partners of pregnant women with syphilis attending ANC has never been tried in Malawi. By engaging both sexual partners

through partner-notification slip plus oral HIVST, the strategy can reduce the risk of syphilis and HIV acquisition or transmission, and subsequent vertical transmission.

Literature Review

Pregnant women are at higher risk of acquiring HIV than their non-pregnant counterparts.[18,19] Biologically, pregnant women are more vulnerable to acquire HIV due to hormonal and immunological changes.[20-24] Additionally, behavioral factors such as condomless sex during pregnancy or breastfeeding and if male partners seek other sexual partners during pregnancy or early days of postpartum increases women susceptibility to HIV infection. Sexually transmitted infections during pregnancy, including syphilis, are associated with increased risk of HIV infection.[25-27] To avert HIV infections among pregnant women, it is important to engage both the pregnant women and their sexual partners in programs that reduce the risk of HIV acquisition and transmission.

Besides increasing the likelihood of exposure to HIV, sexually transmitted diseases such as syphilis are very harmful in pregnancy. Fetus of mothers' with maternal syphilis are at risk of contracting congenital syphilis that can lead to fetal anomalies and miscarriages.[28-30] If the sexual partners of pregnant women are not tested and treated for syphilis, the pregnant women who have been treated for syphilis are still at risk for new syphilis infection from their partners. Encouraging sexual partners of pregnant women with syphilis come to the clinic for syphilis testing and treatment may protect both the pregnant woman and the fetus from syphilis re-infection and infection respectively.

Diagnosis of sexually transmitted infection during pregnancy is an indicator of exposure to someone who is at risk of acquiring and transmitting other STI including HIV. Pregnant women who acquire HIV during pregnancy have acute/early HIV infection (AHI). Women with AHI have high levels and are more likely to transmit HIV to their infants than mothers with established HIV-infection.[31-33] Unfortunately, HIV incidence among pregnant and breastfeeding women is not rare in sub-Saharan Africa, with reported incidence as high as 7% in a study conducted in multiple countries in Southern Africa. To prevent mother-to-child transmission of HIV, HIV-uninfected pregnant women need to be protected from exposure to HIV. When properly implemented, HIV testing in male partners of HIV-uninfected pregnant women will minimize the likelihood of exposure to HIV during pregnancy.

Hypotheses

The overarching hypothesis of this study is that including oral HIV self-testing will increase HIV testing in male partners and decrease the likelihood of pregnant women exposure to HIV.

Specific Aims/Study Objectives

This study has three specific aims related to male partners of HIV-negative women engagement in HIV testing. These are described below:

Aim 1: Compare the acceptability of male partners' engagement in HIV testing using partner-notification slip plus oral HIVST to partner-notification slip only among male partners of HIV-

negative pregnant women with syphilis. We will compare the partner-notification slip plus oral HIVST intervention to partner-notification slip only (standard of care) for increasing the proportion of male partners reporting to clinic and proportion of male partners testing for HIV.

Aim 2: Identify demographic and sexual behavior factors associated with male partners' return to clinic for HIV counselling and testing. We will compare the characteristics of male partners in the intervention arm to the characteristics of those in the standard of care arm to identify factors associated with male partner involvement in HIV testing and counselling.

Aim3: Evaluate if using partner-notification slip plus HIV self-testing among HIV-uninfected pregnant women is associated with any social harm. We will analyse transcripts and structured observation memos using content analysis methodology to identify major themes using established qualitative research methods including principles of triangulation, negative case analysis, and respondent validation.

Methodology

Study Design

This pilot study is a two-arm un-blinded randomized control trial of HIV-negative pregnant women with syphilis attending ANC. Women will be randomized to Standard of Care (SOC) or to an intervention arm. In the SOC arm, women will be given a partner notification slip inviting their male sexual partners for syphilis testing and treatment. Male sexual partners for women in SOC who report to the clinic will be invited to have an HIV test as well. The women in the intervention arm will be given oral HIVST kit for their partner and partner-notification slip inviting their sexual partners for syphilis test and a confirmatory HIV test.

The main outcome will be the proportion of males who will show up to the clinic for HIV counselling and testing within 30 days of issuance of the partner notification slip. All participants will be actively followed up telephone until the male partner shows up to the clinic or 30 days elapses.

Study Setting

The study will be conducted at Bwaila District Hosptial. Bwaila District Hospital is a large maternity hospital serving the greater Lilongwe catchment area. Within Bwaila ANC, women are routinely screened for Syphilis and HIV infection using opt-out individual HIV testing and counselling.

Study Population

This study will comprise of all HIV-negative pregnant women with syphilis attending ANC at Bwaila District Hospital in Lilongwe, Malawi. Pregnant women will be eligible to participate if they meet the following criteria:

Inclusion Criteria

- HIV-negative with syphilis

- ≥18 years old or 15-17 years old and married (emancipated minors per Malawi law)
- Available and willing to be contacted by phone within the next 30 days
- Part of a heterosexual relationship for ≥3 months and expects the sexual partner to be able to come to Bwaila in the next 30 days
- Able and willing to provide informed consent

Exclusion criteria

Any condition that in the opinion of the study investigator would compromise the ability of the prospective participant to provide informed consent, undergo study procedures safely, or would prevent proper conduct of the study.

Study Procedures

Study staff will maintain a screening log with documented reasons for non-eligibility. Women interested in participating will be consented into the study, administered a brief survey, and randomized to one of the two study arms. Women in **both arms** will then be provided with partner-notification slip and encouraged to bring male partners to Bwaila for syphilis testing and treatment. The partner-notification slip will contain a unique identifier for the female participant. Women in both arms will be asked to provide phone number(s) through which they can be contacted.

In addition to partner-notification slip, women in the **intervention arm** will be given oral HIVST kit for their partner that will include manufacturer-provided instructions for use. Women in the intervention arm will be trained on how to conduct the Self-test and will be informed on the performance and limitations of the product. They will also be given contact details and information about HIV testing services if uncertain about how to correctly perform the self-test or interpret the self-test result. The same information will be included in a study brochure that they will take home to the male partners.

Male partners for women in **both arms** who report to the clinic will be offered syphilis and HIV counseling and testing. Male partners for women in the **intervention arm** with a reactive HIV self-test result will be offered confirmatory HIV testing. If the partners for women in **both arms** have confirmed HIV-positive diagnosis, they will be linked to HIV treatment and care. All partners for women in **both arms** with a non-reactive self-test result will be advised to retest later if there is a possibility that they were exposed to HIV in the preceding six weeks, or if they are at high ongoing HIV risk.

The compensation amount for participants will be consistent with other study incentives in this setting ($10).

Data Collection and Management

Qualitative data

We will conduct approximately 10 in-depth interviews with health-care and 10 in-depth interviews with mothers who received the intervention. During the interviews, we will use a

semi-structured questionnaire and all interviews will be tape-recorded and later transcribed from the local language (Chichewa) to English.

Quantitative data

Study staff will be responsible for data collection. Clinic-based staff will screen and consent male and female participants and administer surveys. Participant health information will be recorded on study case report forms (CRFs). All study documents including consent forms and CRFs will be stored in locked filing cabinets. A trained data entry clerk will be responsible for entering data into a password protected Microsoft Access database. All the data entered will be uploaded to a UNC Project server at the end of each working day for backup

Sample Size

We will consecutively enroll HIV-negative pregnant women with syphilis until we reach a convenient total sample of 200 women, with 100 women randomized to each arm. Assuming partner-notification slip uptake of 30% among pregnant women with syphilis, evaluating 200 women will give us 83% power to detect a 20% difference in proportion of male partners reporting to clinic between women randomized to SOC and those randomized to the intervention.

Data Analysis

Aim 1: Compare the acceptability of male partners' engagement in HIV testing using partner-notification slip plus oral HIVST to partner-notification slip only among male partners of HIV-negative pregnant women with syphilis. The main outcomes for this aim will be: 1) number and proportion of male partners testing for HIV. 2) Median time from issuance of notification slip to male partner return to clinic. We will calculate the proportion and the corresponding 95% confidence interval (CI) of male partners coming to clinic. We will also calculate the median and the interquartile range of the time between issuance of partner-notification slip and the return of the male partner to clinic. Two-sample test of proportion and Wilcoxon ranksum test will be used to compare differences in proportion of male partners testing for HIV and differences in median time to return to clinic, respectively.

Aim 2: Identify demographic and sexual behavior factors associated with male partners' return to clinic for HIV counselling and testing. We will identify the factors associated with male-partner involvement in HIV counselling and testing using a questionnaire that will be administered to the pregnant women. We will use numbers and proportion (for categorical variables), and means or medians as appropriate (for continuous variables) to describe the characteristics of our population. Log-binomial regression models will be used to estimate both unadjusted and adjusted risk ratios and their corresponding 95% CI.

Aim3: Evaluate if using partner-notification slip plus HIV self-testing among HIV-uninfected pregnant women is associated with any social harm. We will conduct a qualitative analysis of

in-depth interviews transcripts and research memos from structured observations. To identify major and minor themes that explain those patterns, we will analyse transcripts and structured observation memos using content analysis methodology and appropriate analytical software. In this analysis, we will apply established qualitative research methods including principles of triangulation, negative case analysis, and respondent validation.

Confidentiality/Ethics

Confidentiality Assurance

Sensitive information will be collected from both female and male participants. Measures will be taken to ensure this information is not shared between partners. The information on the notification slip will not disclose that the woman has syphilis. It will simply state that they need to report to the clinic for health information.

Both male and female participants will be assigned a study ID number. This number will be linked to the participant name and medical record at the antenatal clinic only through a separate log book that will be kept in a separate locked file. Data will be double-entered into a password protected Microsoft Access database by a trained data entry clerk. Only the study staff will be able to link the medical record that has the participant name on it with study information that has the study ID number on it. At the conclusion of the study, this link between the name and number will be destroyed. Maganizo Chagomerana, PhD, Principal Investigator, will be responsible for the data and can be reached at +265-99-645-7968.

No subjects will be identified in any report or publication about this study. In some cases, information in this research study could be reviewed by representatives of the University of North Carolina, research sponsors, or Malawi government agencies for purposes such as quality control or safety.

Risks

Participants may feel embarrassed to answer questions about sexual behavior. They can refuse to answer any questions at any time. During the HIV test, participants may feel discomfort when blood is drawn. They may also feel dizzy or faint, or experience bruising or swelling at the blood drawing site. However, this is part of standard of care for HIV counseling and testing. Risk is minimal. Participants may become worried or anxious while waiting for HIV test results. Trained counselors will be available to help participants deal with these feelings either at the clinic or through phone. HIV partner notification may cause social, economic, legal or physical harm but these harms are rare. Our team will do everything in our power to help them resolve these problems if they arise. We will also systematically ask all female participants through telephone if these problems have occurred.

Benefits

The benefits to females from being in this study are to help notify sexual partners that they may have been exposed to syphilis. This study may help male participants learn their syphilis and

HIV status. It will help couples learn each other's HIV and syphilis status. If the male partner has syphilis, he will be able to get treatment. If the male partner is HIV-infected, he will be linked to HIV care or treatment. If the couple is HIV-discordant, they may be able to use behavioral prevention measures to remain HIV-uninfected. Malawi may benefit from the results of this research by learning new knowledge about HIVST and understanding of HIVST within the Option B+ program.

Dissemination of Results

The results of the study will be presented at international scientific meetings and published in scientific journals. The results will also be submitted to the NHSRC. The preliminary data collected in this study may lead to larger longitudinal studies that will enable us further evaluate the impact of partner notification plus HIV self-testing on male partners HIV testing.

Work Plan

Study Activity	**2018**				**2019**										
	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11
Regulatory / IRB submission															
SOP development															
Staff training															
Participants' enrolment															
Data Analysis															
Dissemination of results															

Budget

Item	Amount	# Units	Units	Total
Personnel				
HIV Counselor	$2,400	1	Year	$2,400
Supplies				
ORAquick Test kit	$50	100	Packet	$5,000
Airtime	$300	1	Year	$300
Printing documents	$5	200	Couple	$1,000
Participant incentives	$10	200	Couple	$2,000
Subtotal				$10,700
NHSRC percentage	$10,700	0.1	application	$1,070
NHSRC fee	$150	1	application	150
NHSRC subtotal				$1,220
Total				**$11,920**

Budget justification:
The specific costs for this project include salary support for HIV Counsellor at 100% effort for 1 year. ORAquick HIV Self-test kits will be purchased and given to women who will be randomized to the partner-notification plus oral HIVST arm. We will buy airtime to make follow-up telephone calls to clients. We will also pay for printing materials for partner-notification slips and instructions for self-test in Chichewa. The total budgeted for this project is $11,920.

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