STUDY PROTOCOL

Combination Partner HIV Testing Strategies for
HIV-positive and HIV-negative Pregnant Women:

A Pilot Study

NCT number NCT04124536
Document Date 6/17/2019

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Protocol version 1.2
June 17th 2019

Funded by:
US National Institutes of Health
R01 AI131060
A dyad approach to combination HIV prevention in pregnancy for Zambia and Malawi

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ABBREVIATIONS AND ACRONYMS

ANC	Antenatal care
ART	Antiretroviral therapy
CI	Confidence interval
HIV	Human immunodeficiency virus
SD- HIVST	Secondary distribution of HIV self-test kits
HTS	HIV testing services
IPV	Intimate partner violence
PrEP	Pre-exposure prophylaxis
PMTCT	Prevention of mother to child transmission
RR	Relative risk
SSI	Semi-structured interviews

PROTOCOL SUMMARY

Background: Despite intensive programmatic efforts, a significant proportion of pregnant women in Zambia do not know their partner's HIV status. Being unaware of a partner's HIV status represents a major barrier to HIV prevention and treatment efforts.

Objective: The overall objective of this study is to evaluate whether the addition of secondary distribution HIV self-test kits (SD-HIVST) to existing partner notification guidelines increases the proportion of male partners who access facility-based HIV testing services (HTS), when compared to the partner notification strategy alone.

Design: Two parallel, unmasked, 1:1 pilot randomized controlled trials among pregnant women seeking ANC services in Lusaka, Zambia. We will compare two strategies for HIV testing of partners in parallel trials, one enrolling HIV-positive pregnant women and the other enrolling HIV-negative pregnant women.

Study Arms: Participants randomly assigned to the *control arm* will be asked to identify recent sexual partner(s) and these individuals will then be provided the existing partner notification strategies for HIV testing. Those randomized to the *intervention arm* will receive identical partner notification services; in addition, they will be offered HIV self-test kits (i.e., SD-HIVST)—and instructions on their use—for their partners.

Population: Pregnant women 18 years of age or older over who enter antenatal care (ANC), stratified by HIV status.

Study Site: Chipata Level 1 Hospital in Lusaka, Zambia.

Duration and Follow up: The duration of recruitment is expected to be six months. The length of participant follow-up is 30 days from enrollment.

Study Outcomes: The main outcome will be the proportion of primary male partners who complete facility-based HTS according to participant self-report. The main outcome will be the proportion of primary male partners who complete facility-based HTS according to participant self-report. Secondary outcomes include: proportion of couples (pregnant woman and partner) who receive facility-based HTS together; incidence of social harms and other adverse events associated with the HIV testing approaches; participant uptake preferences and healthcare provider opinions about partner notification services and SD-HIVST; proportion of secondary male partners who complete HIV testing as reported by the pregnant woman; average number of partners tested to identify one HIV-positive partner and average number of SD-HIVST kits distributed to identify one HIV positive partner.

Relevance: To achieve the goal of eliminating mother-to-child transmission of HIV in sub-Saharan Africa by 2030 and to meet the ambitious targets set forth by international agencies (e.g., the "95-95-95" targets from UNAIDS[1]); there is an urgent need to scale up testing. Current guidelines in Zambia recommend both partner notification and SD-HIVST as strategies to increase HIV awareness; however, a combined approach has not been investigated for pregnant women and their partners. Due to the traditionally low rates of partner HIV testing in antenatal settings, such an approach could have immediate policy relevance nationally and regionally.

1.0 INTRODUCTION

Despite the demonstrated effort to increase HIV testing in couples during the antenatal period, HIV testing among male partners of women attending antenatal care (ANC) has remained low.[2] In a systematic review of male partner testing strategies, Hensen and colleagues found rates to be as low as 5% within existing health services.[3] Data from urban Zambia suggests that more than 60% of new infections occur within marriage or cohabiting relationships[4] and 17% of pregnant couples in Lusaka are serodiscordant.[5] Novel ways to engage men in HIV testing are crucial for the prevention of mother-to-child HIV transmission (PMTCT)[6] and heterosexual HIV transmission.

Increasing HIV testing programs in pregnant women has been shown to reduce mother-to-child HIV transmission rates.[14-16] However, the benefit of testing programs extends further than protecting the mother and child. In couples where the female partner is HIV-positive, male partner HIV testing during the antenatal period has been shown to increase ART uptake,[7] adherence,[2] and condom use.[2] Expanding HIV testing services (HTS) to include the male partners of HIV-negative pregnant women may reduce the stigma associated with testing,[8] increase awareness of HIV status, and decrease transmission. Secondary distribution of HIV self-test kits (SD-HIVST), in particular, has been shown to decrease in HIV testing stigma and increase male partner testing outside ANC settings.[9]

We propose parallel pilot randomized controlled trials to assess whether the addition of SD-HIVST to an existing strategy of partner notification increases partner testing in an antenatal setting. Although programs have emphasized such strategies among HIV-positive women, we will evaluate these two strategies (i.e., partner notification alone vs. partner notification plus SD-HIVST) both in HIV-positive and HIV-negative antenatal populations. Understanding the performance, feasibility and acceptability of this strategy among pregnant women and their partners will help to inform broader HIV policy.

2.0 STATEMENT OF THE PROBLEM

PMTCT services have expanded rapidly and dramatically reduced pediatric HIV in sub-Saharan Africa. The rapid progression of scientific, programmatic, and policy advances have moved us closer to the “virtual elimination” of pediatric HIV.[10] In many African settings, acceptance of antenatal HIV testing in health facilities is near universal.[11] Despite the best programmatic efforts, however, a significant proportion of women are unable to bring their partners in for HIV testing and the partner HIV status remains unknown. This represents an important missed opportunity for HIV prevention, care, and treatment.

3.0 RATIONALE

In order to achieve the goal of eliminating mother-to-child transmission of HIV in sub-Saharan Africa by 2030—and to meet the ambitious 95-95-95 target set forth by UNAIDS[1]—new ways are needed to urgently scale up testing and counseling. Current HIV guidelines in Zambia recommend inclusion of HIV testing in routine screening for all pregnant women and their partners.

In antenatal settings, a partner notification approach has been introduced for HIV-positive pregnant women, including client self-referral, provider contract referral, provider referral and/or a dual referral for identified partners. Despite the high HIV incidence rates observed during

pregnancy and breastfeeding,[12] similar recommendations have not been evaluated for women who initially test HIV-negative. In addition, although SD-HIVST has also been endorsed by the Zambian Ministry of Health[13], currently this strategy has not been incorporated into partner notification protocols. Given the general acceptability of SD-HIVST,[14] including in antenatal populations,[9,15] its incorporation has potential to further enhance existing HTS.

The overall objective of this study is to evaluate whether the addition of SD-HIVST to existing partner notification guidelines increases the proportion of male partners who access facility-based HTS, when compared to the partner notification strategy alone. In two parallel randomized trials, we will compare these two HIV testing strategies among partners of HIV- positive and HIV-negative pregnant women.

4.0 LITERATURE REVIEW

4.1 Male partner HIV testing, couples HIV testing and counseling

Increasing male partner HIV testing is recognized as a key component for PMTCT services.[2] Male partner involvement in ANC testing and counseling programs has positive effects on continued ANC attendance,[16,17] PMTCT uptake,[7,18] infant outcomes,[19,20] and uptake of HIV prevention methods such as treatment as prevention[21] and male circumcision.[22] Aluisio and colleagues, for example, found that male involvement in PMTCT could reduce the risk of vertical transmission and the composite risk of infant HIV infection or mortality by as much as 40%.[23]

In sub-Saharan Africa, where men are less likely to know their HIV status compared to women,[7] barriers to HIV testing exist at different levels. In their systematic review Morfaw and colleagues[24] identified factors associated with increased male partners HIV testing in PMTCT programs. These were categorized at the level of the health system, individual, and couple (Table 1). Novel ways to engage men—who often do not access institutional healthcare—in HTS are crucial for the elimination of HIV.[25]

Table 1: Facilitators to male involvement in HIV testing in ANC settings[24]

Health System	Individual	Couples
• Invitation letters • Offering counseling and testing for HIV at alternate sites • Offering counseling and testing for HIV within ANC settings • Availability of personnel to encourage testing and facilitate disclosure • Counseling services during non-working hours • Holding of open discussions on free prenatal testing for partners	• Providing men time to consider PMTCT recommendations • Increased male knowledge of HIV and perceived benefits of PMTCT	• Offering routine couples testing • Discussion of PMTCT within the couple • Change from voluntary counseling and testing to routine testing and counseling • Offering routine couples counseling

The disclosure of HIV status between pregnant women and their partners is critical for HIV prevention and this important process begins with partner HIV testing. Previous studies have shown that when individuals are aware of their HIV status, they are more likely to take measures to reduce their risk of transmitting HIV to others.[26] Couples who access HTS have been shown to benefit through increase relationship cohesion and normalization of HIV status; decrease intimate partner violence and stigma; increase uptake and adherence to antiretroviral therapy; increase relationship cohesion and normalization of HIV status;[27] and decrease IPV and stigma.[28-30]

4.2 Evidenced-based strategies to increase partner HIV testing

A number of promising interventions have been studied to increase couples and male partner testing in ANC settings. Below, we highlight approaches that have garnered recent attention in the medical literature.[2,31] Although each has been shown to be effective in clinical trials and implementation studies, no one approach has reached the high testing thresholds targeted by national programs or international agencies.[1,13,32]

Use of partner notification services, either passive or active, for HIV testing is an established practice supported by a growing body of literature.[33-35] In Malawi, for example, the use of an invitation card increased the chances that a male partner would accompany the pregnant woman to her next antenatal visit (28% vs. 19%, p=0.02).[36] The invitation approach was also found to be acceptable in Tanzania, where 54% of women returned with their partners after being issued an invitation letter; of these, 81% agreed to couples-based HIV testing.[37] In South Africa, male partners receiving an invitation for HIV testing were more likely to undergo male partner testing, compared to those receiving an invitation for a pregnancy information session (32% vs. 11%, RR 2.82, 95% confidence interval [CI]: 2.14–3.72).[38] In a randomized study, Rosenberg, et al. found that an invitation letter with follow-up contact tracing for partners resulted in a higher proportion of HIV testing among male partners compared to the standard of care (74% vs. 52%, p<0.001).[39] Although male partner HIV testing rates were initially similar between the two arms, they increased considerably once contact tracing efforts began.

Another promising approach to increase male partner HIV testing is health care worker delivered home-based testing. This strategy extends the reach of health services into the community and may provide greater convenience and privacy. In Zambia, such activities have been incorporated into partner notification approaches—specifically for provider and dual referral—via community-based healthcare providers. A pair of randomized trials, both from Kenya, supports these findings. At 6 weeks postpartum, Osoti and colleagues reported higher rates of male partner engagement (89% vs. 37%, p<0.001) and male partner HIV testing (85% vs. 36%, p<0.001) in the home-based visit arm, compared to a clinic invitation alone.[40] In secondary analysis, both the pregnant participants (54%) and male partners (68%) preferred home-based testing to traditional venues such as ANC or voluntary HIV testing and counseling sites. The majority (81% of men and 65% of women) would recommend this testing approach to others.[41] Krakowiak[42] and colleagues reported similar findings. At 6 months postpartum, home-based education and HIV testing were associated with higher male partner testing (RR: 2.10, 95%CI: 1.81–2.42), testing as a couple (RR: 3.17, 95%CI: 2.53–3.98), and knowledge of male partner HIV status (RR: 3.38, 95%CI: 1.70–6.71), compared to clinic invitation alone.[43] The intervention was also shown to be cost-effective in formal analyses.[44]

Secondary distribution of HIV self-testing kits (SD-HIVST) is currently endorsed by the World Health Organization and Zambian HIV testing guidelines. [13,35] SD-HIVST is associated with an increased uptake and frequency of testing[45] and it has the potential to increase HIV disclosure within couples. Benefits of the SD-HIVST strategy include increased convenience, shorter turnaround time for results, improved testing privacy, and greater sense of autonomy.[9,46,47] Additionally, SD-HIVST has been shown to reduce fears regarding lack of confidentiality and potential stigma and to increase facility-based confirmatory testing in male partners.[46,48,49] In a recent survey study of adolescents and adults in Lusaka SD-HIVST was found to be acceptable and scale up of their use was recommended.[9] SD-HIVST to pregnant women, for use by their male partners, is a relatively new approach, but early findings have been encouraging. In Kenya, a cohort study found the approach to be acceptable, with high proportions of distribution of self-tests to partners during pregnancy (91%) and postpartum (86%).[46] Although IPV was infrequent following the distribution of self-test kits (2 of 91 postpartum women, 0 of 53 antenatal participants), women who reported recent physical or sexual violence were less likely to report partner testing (adjusted RR: 0.10, 95%CI: 0.12–0.87) or couples testing (adjusted RR: 0.13, 95%CI: 0.03–0.54).[50] Results from a randomized study found that the SD-HIVST kits to partners of a HIV positive index patient achieved higher reported partner testing rates than clinic invitation alone (91% vs. 52%, p<0.001).[51] In this study, no participants reported IPV due to HIV testing.[51] In a recent survey study of adolescents and adults in Lusaka HIVST were found to be desirable and acceptable[9] Further research is needed the regarding most efficient and effective use of this public health intervention in ANC settings.

4.3 Our formative work

Women in sub-Saharan Africa face an unacceptably high risk of acquiring HIV during pregnancy and breastfeeding. In a meta-analysis of 19 studies, Drake and colleagues reported a pooled incidence rate of 4.7/100 person-years (PY) (95%CI: 3.3–6.1) during pregnancy and 2.9/100 PY (95%CI: 1.8–4.0) while breastfeeding.[12] During our formative research, we completed a new systematic review and meta-analysis to estimate the risk of HIV acquisition during pregnancy and the postpartum period in sub-Saharan Africa. Overall, 41 studies met our inclusion criteria. These represented 35 independent cohorts that contributed over 100,000 PY of follow-up. The

pooled HIV incidence rate during pregnancy and the postpartum period was 3.7/100PY (95% CI: 3.0-4.5), with no detected difference between pregnant and postpartum periods. This pooled incidence rate is consistent with cohort studies of female sex workers, men who have sex with men, and HIV serodiscordant couples.[52-56]

We have developed a framework for HIV prevention during pregnancy and breastfeeding. In our framework (Figure 1), partner HIV status is used to stratify the population into six distinct groups (A-F). To optimally reduce horizontal and vertical HIV transmission during pregnancy, we argue that tailored interventions are needed. We hypothesized that three specific points along this dyad-based framework could have important downstream impact: (1) male partner HIV testing, (2) support for ART adherence, and (3) support for PrEP during pregnancy.

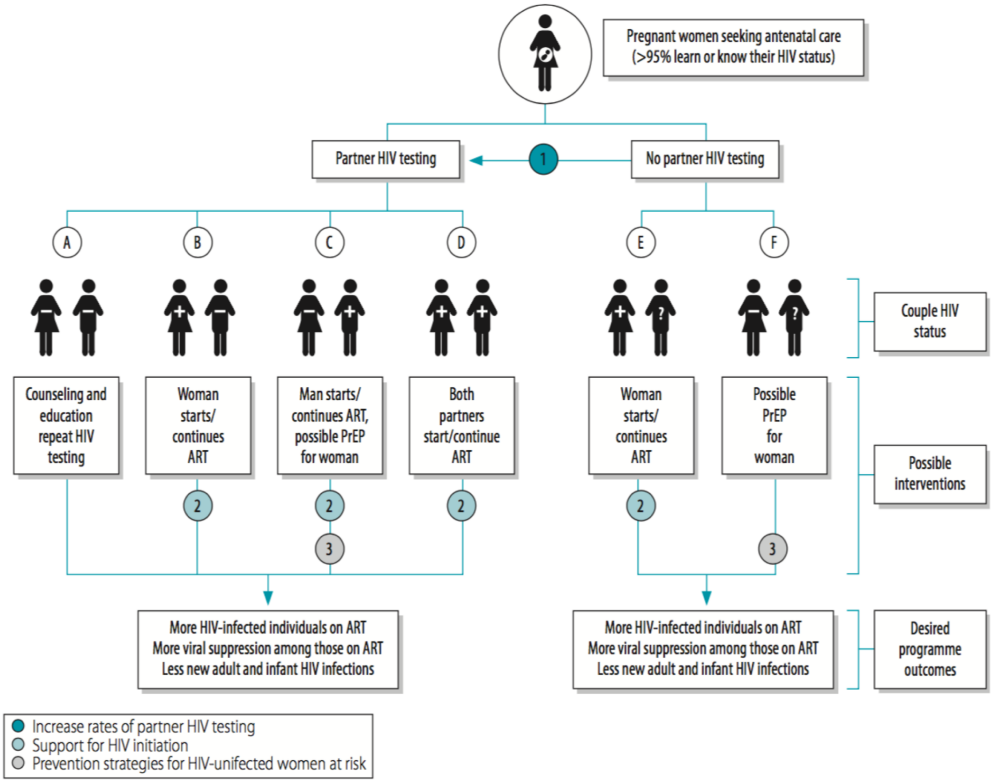

Figure 1: Proposed framework for HIV prevention during pregnancy[57]

To test this hypothesis, we developed a mathematical model describing horizontal and vertical HIV transmission during pregnancy within patient-partner and patient-infant dyads, respectively. The model was on based biological and behavioral inputs from literature estimates and ANC program data from Malawi and Zambia. The downstream impact of three main HIV prevention strategies, alone and in combination, was assessed by varying: (1) male partner HIV testing from a base-case value of 15% to a target of 35%; (2) suppressive ART for HIV-positive ANC patients and partners from a base-case of 70% to a target of 90%; and (3) adherent PrEP use for HIV-uninfected female ANC patients from a base-case of 0% to a target of 20%. Using this model, the percentage of horizontal and vertical HIV infections that could be averted relative to the current (base-case) scenario (see Table 2) were estimated as follows:

- Increasing male partner testing to 35% coverage was predicted to reduce horizontal and vertical transmissions by 16.7% and 15.1%, respectively (scenario 2); corresponding reductions with 20% female PrEP use were 13.4% and 12.1% (scenario 4).
- Jointly increasing coverage of both male partner testing and female PrEP use by 20 percentage points was predicted to reduce horizontal and vertical transmissions by ~one-quarter (scenario 7); this reduction increased to ~one-third with a combination of these two interventions plus increasing suppressive ART (scenario 8).
- Across scenarios, a 20-percentage-point increase in suppressive ART for HIV-positive patients and partners had only a modest incremental impact (scenarios 3 vs. 1, 5 vs. 2, 6 vs. 4, 8 vs. 7).

The modeling suggests that combination HIV prevention in ANC settings, particularly approaches that increase male partner testing and female PrEP use, could substantially reduce HIV incidence among pregnant women, their partners, and their newborns in sub-Saharan Africa.

Table 2: Percentage of potential horizontal and vertical HIV infections averted

Scenario	% ANC patients' male partners tested for HIV	% HIV+ ANC patients & partners on suppressive ART	% HIV− female ANC patients on PrEP	% Horizontal transmissions* averted	% Vertical transmissions averted
1	Current (15%)	Current (70%)	Current (0%)	--- (Base case)	--- (Base case)
2	↑ to 35%	Current (70%)	Current (0%)	16.7%	15.1%
3	Current (15%)	↑ to 90%	Current (0%)	1.1%	1.8%
4	Current (15%)	Current (70%)	↑ to 20%	13.4%	12.1%
5	↑ to 35%	↑ to 90%	Current (0%)	21.5%	19.9%
6	Current (15%)	↑ to 90%	↑ to 20%	16.3%	13.9%
7	↑ to 35%	Current (70%)	↑ to 20%	27.8%	25.1%
8	↑ to 35%	↑ to 90%	↑ to 20%	32.1%	29.2%

* both female-to-male and male-to-female

As part of our formative work, we also conducted qualitative research to better understand preferences for partner HIV testing. A total of 145 semi-structured interviews were conducted with pregnant women, their male partners, health care workers, and policymakers in Zambia and Malawi. Preliminary results indicated that novel testing modalities were considered acceptable; there did not appear to be a strong preference for one particular modality for male partner HIV testing. Convenience and the availability of alternate testing venues were viewed favorably by participants. Universally, concerns were raised about the potential for relationship conflict, including IPV, arising from the invitation for HIV testing.

5.0 RESEARCH QUESTION

In the antenatal setting, does the addition of SD-HIVST to existing guidelines for partner notification increase the proportion of male partners who access facility-based HTS?

6.0 OBJECTIVES AND OUTCOMES

The overall objective of this study is to evaluate whether the addition of SD-HIVST to existing partner notification guidelines increases the proportion of male partners who access facility-based HTS, when compared to the partner notification strategy alone. In two parallel randomized trials, we will compare the two HIV testing strategies among partners of HIV- positive and HIV-negative pregnant women.

6.1 Primary and secondary objectives

Our primary objective is:

1) To evaluate whether a combination of partner notification plus SD-HIVST increases primary male partner HIV testing when compared to partner notification alone.

Our secondary objectives are:

1) To evaluate whether a combination of partner notification plus SD-HIVST increases couple HIV testing when compared to partner notification alone.
2) To identify social harms and other adverse events associated with the HIV testing approaches.
3) To explore acceptability and feasibility of partner notification and SD-HIVST among female participants and healthcare workers.

Our exploratory objectives are:

1) To evaluate whether a combination of partner notification plus SD-HIVST increases HIV testing among secondary male partners when compared to partner notification alone.
2) To estimate the relative yield of identifying HIV-positive partners with each partner HIV testing strategy.

6.2 Study Outcomes

Our primary outcome is:

- Proportion of primary male partners who complete facility-based HTS by participant self-report. The current Zambian guidelines require confirmatory testing by a trained healthcare provider following HIV self-testing. The requirement of facility-based HTS ensures that testing is performed appropriately and that counseling messages are provided according to current guidelines.

Our secondary outcomes include:

- Proportion of couples (pregnant woman and partner) who receive facility-based HTS together.
- Incidence of social harms and other adverse events associated with the HIV testing approaches.
- Participant uptake, preferences and healthcare provider opinions about partner notification services and SD-HIVST.
- Proportion of secondary male partners who complete HIV testing as reported by the pregnant woman.
- Average number of partners tested to identify one HIV-positive partner.
  Average number of SD-HIVST kits distributed to identify one HIV positive partner.

7.0 HYPOTHESES

1) For both HIV-positive and HIV-negative women, the addition of SD-HIVST to partner notification will increase the proportion of primary male partners who access HTS.
2) For both HIV-positive and HIV-negative women, the addition of SD-HIVST to partner notification will increase the proportion of couples who access HTS.
3) The addition of SD-HIVST to partner notification will not increase the incidence of reported social harms.
4) For both HIV-positive and HIV-negative women, SD-HIVST will be acceptable to patients and feasible in antenatal care settings.

8.0 METHODOLOGY

8.1 Study design

Two parallel, unmasked, 1:1 pilot randomized controlled trials among pregnant women seeking ANC services in Lusaka, Zambia. We will compare partner HIV testing uptake using partner notification only and partner notification plus SD-HIVST, among partners of HIV-positive and HIV-negative pregnant women.

8.2 Study site and study population

Chipata Level 1 Hospital is a government health facility run by the Lusaka District Health Management. Serving a population of over 100,000, the ANC clinic is very busy, with an average of 400-450 new patients and 900-1000 return visits each month. Similar to other health facilities in the Lusaka district, the HIV prevalence in the antenatal clinic is ~10-15%.

8.3 Selection of Participants

We will recruit women receiving ANC who meet the following criteria:

- 18 years of age or older
- Pregnant at time of enrollment based on antenatal record
- Documented HIV status (either positive or negative) in antenatal record
- Reports at least one current sexual partner
- Willingness to provide her own contact information
- Ability and willingness to provide informed consent
- Intent to remain in current geographical area of residence for the duration of follow-up activities
- Willingness to adhere to study procedures

Women who express concerns about IPV or social harms as a result of participation during the screening process will not be included. Women who have previously enrolled in the study will not be permitted to enroll again.
Following informed consent, participants will be enrolled into one of two parallel randomized trials based on their HIV status.

8.4 Study Intervention

All women enrolled will receive partner notification services based on the current recommendations for HIV positive women in ANC settings.[13] This includes the elicitation of primary and secondary male partners via interview with the pregnant woman. According to the 2018 Zambian Consolidated HIV Guidelines[13], four types of partner notification should be offered:

- **Client self-referra**l - clients are encouraged by providers to disclose their HIV status to their sexual partner(s) by themselves, and to suggest HTS to the partner(s)
- **Provider contract referral** - clients enter into a contract with a trained provider and agree to disclose their status by themselves and to refer their partner(s) to HTS within a specific time period. If the partner(s) of the HIV-positive individual do not access HTS or contact the health provider within that period, then the provider will contact the partner(s) directly and offer voluntary HTS.
- **Provider referral** - the health care provider confidentially contacts the person's partner(s) directly and offers the partner(s) voluntary HTS.
- **Dual referral** – a health care provider accompanies and provides support to clients when they disclose their status to their partner(s). The provider also offers HTS to the partner(s).

While partner notification is currently offered to HIV-positive pregnant women only, in this study we will also adapt these referral services for pregnant women testing HIV-negative.

HIV-positive and HIV-negative participants in the intervention arms will be offered SD-HIVST in addition to partner notification. The HIV self-test kits are oral swabs and are currently included in the Zambian national guidelines for HIV testing. We will be offering an integrated strategy of both partner notification and SD-HIVST. Participants will be instructed on the use of the HIV-self-test kits at home or alternative site,[13] and provided HIV self-test kits for themselves and each reported sexual partner. The SD-HIVST will be promoted as a screening test; regardless of the results—and according to the Zambian HIV guidelines—all participants will be strongly encouraged to receive HTS at the study clinic. The women will receive verbal and written instructions on the use of an HIVST as per current guidelines.[13] This will include:

1) How to perform the test and interpret the result correctly;
2) Where to access HIV testing services and further support services; and
3) How to safely dispose of the used test-kits.

8.5 Recruitment and enrollment procedures

Staff will provide interested participants with additional information and referral to the study. Potential participants will be identified at any point in their pregnancy. All women attending the ANC clinic at Chipata Level 1 Hospital who meet the eligibility criteria as listed in section 8.3 will be invited to participate in the study.

All participants will undergo an informed consent procedure to ensure they are well-informed about the study, its objectives, and its requirements (section 9.2). After informed consent is obtained, we will collect social, demographic, medical, and behavioral information from all participants. We will obtain from the pregnant woman locator information—including phone

numbers, addresses, and directions—for her and her partner. Information about partner(s) will be collected as reported by the female participant.

Participants will be randomly assigned to one of two study arms. The study statistician will use statistical software to generate a list of random assignments with a 1:1 ratio. The randomly generated numbers will be placed in opaque sealed envelopes and sequentially numbered with participant identification numbers[58].

All participants will be asked to identify sexual partner(s). Participants with multiple partners will be asked to designate their primary partner—defined as whomever the participant designates as their primary partner, e.g. husband or boyfriend—and secondary partners—defined as any other sexual partners. Study staff will discuss the partner notification strategies (see section 8.4) for each partner and help the participant to devise a partner notification plan.

Participants assigned to the intervention arm will receive structured counseling about HIVST and its potential role in engaging male partners in HIV testing. These women will be offered oral HIV self-test kits, one for themselves and one for each reported partner. For those who agree to try SD-HIVST, clinic staff will provide instructions about their use, their interpretation, and disposal of used test kits, as per current Zambian guidelines (see section 8.4). We will emphasize the role of the oral HIV self-testing kits as a screening measure and the need for facility-based confirmatory testing.

Regardless of study arm, participants and their partners will be encouraged to complete facility-based HTS as soon as possible—ideally in the first two weeks and within the first 30 days (our primary outcome). Participants will be given a schedule of possible times for facility-based HTS at the study site. These will include regular clinic hours; based on participant demand, we may add weekend and/or off-hour time periods. Such services would be equally available to participants randomized to either study arm. Participants who experience any social harms for example, experiencing emotional, economic, legal or physical harm from a family member, friend, people at work, police officer or other people will be asked to return earlier and provided a designated study contact number for emergencies.

Prior to discharge, all participants will be given a follow-up appointment at 30 days. We will emphasize the importance of this exit visit, even if their partners did not complete HTS or use the HIV self-test kit.

8.6 Study follow-up

At approximately 30 days from enrollment, participants will be asked to return for an exit visit. We will collect information about their experience with the partner notification strategies and whether their partners completed facility-based HTS either at the study or an alternate site. We will ask about any perceived social harms and their potential association with the partner notification strategies or SD-HIVST. For those in the intervention arm, we will also collect quantitative information about SD-HIVST, including acceptability, preferences, and actual use. This information will be collected at the end of the visit, after other measures pertaining to both arms are collected. A random sample of these women (HIV-positive and HIV-negative) from both arms will be invited to participate in the qualitative research component (see section 8.9).

8.7 Retention

Once participants are enrolled in the trial, the study team will make efforts to retain them in follow-up to minimize bias associated with loss to follow-up. Given the relatively short follow-up duration for follow-up (30 days), we expect this to be achievable. The study team will closely monitor retention rates and address any issues prospectively. Strategies to minimize attrition include:

- Thorough explanation of the study visit schedule and procedures during informed consent.
- Collection of detailed locator information at enrollment.
- Use of appropriate and timely visit reminder mechanisms (including phone calls and text messages, if participants specifically agree).
- Follow-up after missed visits, including home or alternative, off-site visits if agreed upon.
- Mobilization of trained outreach workers to complete in-person contact with participants at their homes and/or other locations.

If participants elect to discontinue their involvement in the study, we will document their stated reason(s). These will be reported in any reports about the study cohort.

8.8 Safety Monitoring

At each study visit, study staff will evaluate participants for social harms. A social harm will be defined as a non-medical untoward consequence of study participation, including difficulties in personal relationships, stigma, or discrimination from family or community. We will use standardized instruments to screen for these adverse events, with follow-up counseling and/or support as needed. For severe cases, we will make referrals to local government agencies and provide additional resources (e.g., transport) to minimize barriers to seeking out such services.

8.9 Qualitative Interviews

To provide a more in-depth understanding of the acceptability and feasibility of the HIV testing strategy we will recruit up to 20 participants from each arm (40 overall) to participate in semi-structured interviews (SSIs). Within each study arm, up to 20 will be HIV-negative participants and up to 20 will be HIV-positive participants. In order to provide insight into the factors that affect male partner HIV testing, we will interview women from both arms whose partners did or did not complete HIV testing, see Table 3.

In addition, to gain insight into the feasibility of the intervention, we will also conduct SSIs with healthcare workers engaged in providing the study intervention. We will recruit up to 10 healthcare workers to participate in SSI. Selected healthcare workers (including study personnel) should be involved in the counseling and instruction for combined partner notification-HIVST arm.

All participants must be age 18 years or older and demonstrate the ability and willingness to provide informed consent. Additional eligibility criteria for women are listed in Section 9.2. The SSIs will be conducted in rooms at or near the clinic that provide sufficient privacy to ensure confidentiality of information and are quiet enough to enable audio recording of the interviews. Trained female Zambian interviewers will use interview guides to explore key themes, including the acceptability of the HIV testing approach, barriers and facilitators to the approach, and

potential social harms. The SSIs will explore participants' experiences with the HIV testing approach. Each SSI is expected to last 30-60 minutes.

Table 3 SSI Interviews per arm

	HIV+ participant	HIV- participant
Control arm		
Partner tested	5	5
Partner did not test	5	5
Intervention Arm		
Partner tested	5	5
Partner did not test	5	5
Total	20	20

8.10 Pre-intervention Phase

Prior to activation of the main study, we will implement a pre-intervention phase for both HIV-positive and HIV-negative pregnant women. We will recruit women meeting the eligibility criteria for the main study (Section 8.3). Similar to those participants, these individuals will be educated about the study; provide informed consent; answer specific questions about HIV testing history and sexual risk behaviors; and then return approximately 30 days later to report partner HIV testing. We will not provide any interventions for partner HIV testing as described in Section 8.4. Instead, we will educate women about partner HIV testing and encourage them to utilize existing clinical services at the study facility. Overall, we plan to enroll up to 100 participants in this pre-intervention phase, split between HIV-positive and HIV-negative pregnant women. Based on antenatal clinic volumes at Chipata District Hospital, the duration of enrollment for this pre-intervention phase is expected to be 4-8 weeks.

This pre-intervention phase is intended to accomplish two goals. First, it will allow the study team to refine study procedures— including recruitment, informed consent, data collection, and follow-up— prior to the full enrollment of the main study. Second, this exercise will allow us to gather important preliminary data about partner HIV testing within the current standard of care. Although not powered for precision or specific comparisons, this preliminary data will help us to understand the impact of partner HIV testing procedures offered in the study clinic. These data will be used to provide context to the main trial, but are not part of the *a priori* comparisons in the analysis plan.

8.11 Data Management and Storage

Data collected from each participant will include sociodemographic information, relevant HIV and obstetrical history, and results of HIV testing. Study data management (e.g., data transmission, query resolution, etc.) will follow site data management standard operating procedures. Study identification numbers will be used on all forms and communications related to the study. A separate confidential register will link study identification numbers and participant names. All data instruments and registers will be securely stored. Data will be entered into a custom-built database and will be validated via double entry. Computers will be password protected and their access restricted to authorized study personnel. Backups of the data will be made on a weekly basis. Data may be transmitted electronically to the study investigators through secure cloud-

based servers. Study information will not be released without written permission of the participant, except when necessary for monitoring by the relevant ethical committees or their designees. Data will be disposed of following sponsor recommendations. Data will be disposed of after completion of the study per sponsor guidelines. At that time, electronic records, including linkage codes and identifiers, will be deleted. Paper records will be shredded prior to disposal.

8.12 Sample Size

We propose two randomized trials, each based on the pregnant women's HIV status. Enrollment into two parallel trials—rather than single trial with pre-defined strata—is justified by our expectation of different baseline HIV testing rates in the control arm and the potential for different effect sizes according to the pregnant women's HIV status. Our sample size calculations are guided by three main considerations:

(i) In this pilot phase, the studies are powered to detect large, transformative differences in partner HIV testing rates, while evaluating feasibility and acceptability of the interventions.

(ii) While we make educated assumptions about the baseline HIV testing rates in the control arm for both HIV-positive and HIV-negative women, there are currently a dearth of reliable data about HIV testing rates following partner notification, particularly in a programmatic settings. If the intervention were shown to be clinically promising (regardless of statistical "significance"), point estimates and confidence intervals from the pilot trial will help us to inform the design of a larger definitive study.

(iii) In line with the objectives of a pilot study, we seek to obtain preliminary results in relatively short period of time. The sample sizes also consider the capacity for enrollment over a six-month window, based on known ANC patient volumes and HIV prevalence among the antenatal population.

In the trial of **HIV-positive pregnant women**, we anticipate 20% of male partners will test under the partner notification strategy alone (i.e., the control arm). With the addition of SD-HIVST, we expect to see a 25% absolute increase (i.e., to 45%) in partner HIV testing rates. With a significance level of 0.05, power of 80%, and an adjustment for 5% missing data and attrition, we will enroll 116 total HIV-positive pregnant women into the trial (58 per arm).

In the trial of **HIV-negative pregnant women**, we anticipate 10% of male partners will test under the partner notification strategy alone (i.e., the control arm). With the addition of SD-HIVST, we expect to see a 15% absolute increase (i.e., to 25%) in partner HIV testing rates. With a significance level of 0.05, power of 80%, and an adjustment for 5% missing data and attrition, we will enroll 210 total HIV-negative pregnant women into the trial (105 per arm).

We recognize there is uncertainty about baseline partner testing rates for both proposed trials. Among HIV-positive pregnant women, partner notification services have been implemented, but were only recently introduced. For this reason, there are few reliable data about its uptake in the programmatic setting. To our knowledge, partner notification approaches—as proposed in this study—have not been previously studied in HIV-negative pregnant populations. As a result, no empiric data about its uptake currently exist. For this reason, for both trials, we show the calculated power across a range of assumptions for the control arm and a range of possible effect sizes in Table 4.

Table 4. Statistical power and precision for male partner HIV testing RCTs

Population	N enrolled total[&]	N evaluable per arm	Assumed probability of partner HIV testing: Control	Assumed probability of partner HIV testing: Intervention	Power[@]	Example results (in expectation) N tested / N evaluable (%): Intervention	Example results (in expectation) N tested / N evaluable (%): Control	Difference in probabilities (95% CI)
HIV positive women	116	55	20%	40%	63%	22/55 (40%)	11/55 (20%)	20 (3.1, 37%)
				45%	**80%**	**25/55 (45%)**	**11/55 (20%)**	**25 (8.4, 42%)**
				50%	91%	28/55 (51%)	11/55 (20%)	31 (14, 48%)
HIV negative women	210	99	10%	22%	64%	22/99 (22%)	10/99 (10%)	12 (2.0, 22%)
				25%	**80%**	**25/99 (25%)**	**10/99 (10%)**	**15 (4.7, 26%)**
				30%	94%	30/99 (30%)	10/99 (10%)	20 (9.3, 31%)

[&] Assuming 5% missing data / attrition (e.g., loss-to-follow-up). [@] Significance level, alpha = 0.05, using a likelihood ratio chi-square test for two proportions (Power Procedure, SAS/STAT version 14.3)

The targeted effect sizes between the two trials differ. In order to inform Zambia HIV testing guidelines among HIV-positive pregnant women, the effect size would need to be higher to justify further investment into the partner notification plus SD-HIVST. We have powered the trial for HIV-negative pregnant women to detect smaller absolute differences in testing rates (15% difference) because a dearth of empiric data exists for partner notification-based strategies in this population, with or without SD-HIVST. Also, based on our formative research, we reasoned that partners of HIV-negative pregnant women may have comparatively lower motivation for returning to the clinic for facility-based HTS, especially if HIV self-testing outside the clinic was HIV-negative.

8.13 Data Analysis Plan

8.13.1 General Approach:

Two randomized controlled trials will be conducted simultaneously, for HIV positive and HIV negative pregnant women, separately. All primary and secondary endpoints will be evaluated separately for each trial, unless stated otherwise. We anticipate the RCT of HIV negative women may enroll and complete sooner than the RCT for HIV positive women. In the unanticipated case that results are homogeneous between the two trials with respect to the estimated risk difference, and policy implications are similar for the two populations, the two trials can be combined in a weighted analysis to generalize the findings to the target population of pregnant women in Zambia (or Lusaka, more specifically).[59,60] In such a weighted analysis, we anticipate the HIV negative women would have higher weights (on average) to account for the overrepresentation of HIV positive women in the combined trials, as compared to the target population of pregnant women. Additional patient characteristics available in the larger ANC population would also be used for estimating generalizability weights.

Given the pilot nature of these studies, emphasis will be put on estimation and precision of measured effects, rather than null hypothesis testing. An alpha=0.05 significance level will be used throughout (i.e., 95% confidence intervals) with no adjustment for multiple testing. Missing data are anticipated to be uncommon (≤5% missing); a complete case analysis will be used unless the missing data proportion is >10%. In the case of missing data for >10% of individuals, inverse probability weighting for missingness or multiple imputation will be used to account for data missing at random (missing conditional upon measured covariates and outcomes). Missing data patterns will be evaluated blinded to study arm and outcome. If data are suspected to be missing not at random, this will be described with the study results as a limitation.

Analyses will be conducted using an intention-to-treat approach, with women analyzed according to the arm they were randomly assigned to regardless of their subsequent use or non-use of the SD-HIVST kits. The post-randomization use of SD-HIVST kits is a participant or couple-driven choice and will be recorded in both arms. If there is unanticipated cross-over or lack of SD-HIVST uptake, exploratory analyses may use marginal structural models to estimate an "as-treated" effect of SD-HIVST uptake upon the primary endpoint.

8.13.2 Analysis of the Primary Endpoint

The proportion of *primary male partners* who complete facility-based HTS within 30 days of enrollment will be compared between study arms using an estimated difference in probabilities (i.e., risk difference) and a corresponding 95% CI (with the control arm as the referent group). The primary outcome is measured by participant self-report and the partner recorded as the *primary male partner* will be pre-specified before randomization. An adjusted analysis will be conducted using a linear-binomial model to account for chance imbalances in key male partner characteristics (e.g., perceived engagement in index participant's healthcare, distance from home to nearest health facility, day-time work schedule) that may influence HIV testing behaviors.

We will further evaluate our primary outcome (i.e., facility-based HTS) using a time-to-event analysis over the 30-day follow-up, comparing between the two study arms descriptively using Kaplan-Meier curves. A Cox proportional hazards model or restricted mean survival time analysis[61,62] will be used for covariate adjusted analyses and formal comparison between the study arms.

8.13.3 Analysis of Secondary Endpoints

The proportion of *couples* who receive facility-based HTS will be analyzed using the same approach as described above for the primary endpoint. A *couple* receiving facility-based HTS will be defined as both members of the couple participating in HTS together.

In secondary analyses, facility-based HTS and HIVST uptake will be evaluated among all sexual partners (primary and secondary) reported to the study, and will be handled as clustered binary data. These outcomes will be either directly observed by the study staff or self-reported by the pregnant woman participating in the study. Multiple partners of the same pregnant woman will be handled as a cluster using generalized estimating equations (GEE); the analysis will be conducted at the partner level.[62] If feasible, a linear-binomial model fit with GEE will be used; otherwise a probability ratio (i.e., risk ratio) will be estimated using a log-binomial model fit with GEE. The mean (arithmetic average) number of partners tested to identify one HIV positive partner will be estimated with a corresponding 95% CI among all male partners (with the control

and intervention arms pooled, and also summarized by arm). This analysis will also be conducted among solely primary partners. The arithmetic mean number of SD-HIVST kits distributed to identify one HIV positive partner will be estimated with a corresponding 95% CI among the intervention arm only; this analysis will take into account all HIVST kits given to the women, including those she might use to retest her own status.

Incidence of social harms and other adverse events associated with the partner notification or SD-HIVST approaches will be estimated and individual events will be described using line listings. Participant uptake and preferences and healthcare provider opinions about partner notification services and SD-HIVST will be described using frequency tables and summary statistics. Retention in the study for 30 days of follow-up will be described using frequency tables, and reasons for study drop-out will be tabulated. Any participant deaths will be recorded along with the contributing cause(s) of death.

8.14 Analysis: qualitative component

The SSI audio recordings will be transcribed and translated for analysis. All identifiers will be redacted from the interview transcripts prior to analysis. Although we propose sample sizes for each group based on prior experience, the final number interviewed will be determined by theoretical saturation. Data will be analyzed using techniques that include coding, memoing, and matrices to summarize and interpret key patterns in the data. Comparative and thematic analyses will be used to provide an in-depth understanding of the experiences related to HIV testing.

9.0 ETHICAL CONSIDERATIONS

9.1 Ethical approval

All study participants will be fully informed of the study procedures described above. Ethical approval for this study will be sought from the UNZA Ethical Review Committee and the Institutional Review Board at UNC. Ethical approval will also be sought from the National Health Authority in accordance with the National Health Research Act.

9.2 Informed consent

All participants will be consented prior to participation and during the consent process they will be reminded that their participation is voluntary. Discussions with prospective participants and informed consent procedures will be conducted in private to protect patient confidentiality. We will obtain written informed consent from all participants. The study procedures, risks, and benefits will be discussed and we will answer all questions prior to obtaining consent. The consent forms will be translated into local languages (Nyanja and Bemba) and back-translated into English to assure accurate translation. For illiterate participants, a literate impartial witness will be present during the entire consent process to ensure that all of the relevant information has been provided and the participant voluntarily gives consent. Eligible women who do not wish to participate in this study will continue to receive HIV and ANC treatment according to local clinical standards. We will obtain signed permission from the pregnant woman to collect locator information—including phone numbers, addresses, and directions—for her and her partner. Permission for collection of locator information and contract tracing will be per usual practice at the clinic.

9.3 Data storage

The confidentiality of all study records will be safeguarded to the extent legally possible. To maintain participant confidentiality, all laboratory specimens, reports, study data and administrative forms will be identified by a coded number only. All databases will be secured with password-protected access systems, and computer entries will be identified by coded number only. Forms, lists, logbooks, appointment books, and any other listings or data forms that link participant ID numbers to other identifying information will be stored in a separate, locked fireproof safe cabinet in a locked local office. For the data collected through audio recordings, all audio files will be deleted from the recorders after data are transferred into a computer. The computers together with audio tapes, field notes, and all other study materials will be kept in a locked, fireproof safe cabinet in a locked local office. All data analysis will be performed using datasets which have only study ID numbers as unique identifiers.

9.4 Confidentiality

Measures will be taken to ensure safety of data and confidentiality of all our study participants. All participants will be assigned a unique study ID number. The interview guides will not capture names of the participants but only their ID number. No study participant will be identified in any report or publication about this study. However, for quality control and safety purposes, data that we collect may be reviewed by the sponsor of this study (i.e. United States National Institute of Allergy and Infectious Diseases), the ethical and regulatory committees in Zambia, and at the University of North Carolina at Chapel Hill. Clinical information with individual identifiers will not be released without the written permission of the participant. We expect these procedures to adequately protect participant confidentiality.

9.5 Potential risks of proposed research to study participants

Risks to participants in this study are minimal and do not differ significantly from the risks inherent in the local standard of care for pregnant women, their partners, and their infants. Oral HIV-self test kits are currently included in the Zambian national guidelines and are being utilized in programmatic settings. As such, their use outside of research settings should not pose additional risk. In addition, the importance of confirmatory HIV testing at a health facility will be emphasized to all study participants. This approach is recommended by the national HIV testing policy and serves as the primary outcome of our study. In this way, the risk of inaccurate HIV test results should be minimized. In addition, we do not expect more than minimal risks during the one-on-one interview. Participants may feel uncomfortable when being interviewed, but will have the opportunity to skip or refuse to answer any questions that they do not want to answer. It is expected that this study will expose subjects to minimal risks.

Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions, particularly when discussing HIV infection or sexual behaviors. At each step in the study, we will protect participant privacy and confidentiality to reduce these risks (e.g., consenting participants in a private setting, not including names on case report forms, etc.). Although investigators will make every effort to protect participant privacy and confidentiality, it is possible that participant involvement in the study could become known to others, and that social harms may result (i.e., as participants could become known as HIV-infected). There is a risk that sexual partners will react adversely to the participants' suggestions of self-test usage, or to the test result itself. To minimize this risk, we will provide detailed information on the need for confirmatory testing and the availability of HIV care and treatment for HIV-infected persons. Participants will also be given a phone number they can call at any

time if they need assistance or feel they are at risk of harm. We will not enroll women who self-report concern that their partner may hurt them if they suggest using the HIV self-test or home-based testing and in addition we will refer men and women who experience violence to IPV services.

9.6 Potential benefits of proposed research to study participants and others

The benefits to participants include increased knowledge about their partner's HIV status, which in turn may serve to reduce their own, their partner's and their infant's risk of HIV infection. The knowledge gained from this study will also help inform policy makers and HIV prevention programs about the potential role that expanding HIV testing services can play in increasing awareness of HIV status and reducing the number of new HIV infections.

9.7 Inclusion of children, sub-populations, and vulnerable populations

This study focuses on the outcomes of pregnant women and their partners. Newborn infants are not included in the study per se, though they may derive indirect benefit from participation via increased partner HIV testing. Prisoners will be excluded as they receive care at separate facilities.

9.8 Reimbursement/compensation

There is no cost to participating in the study. Participants completing the exit questionnaire will be provided transport reimbursement that will be approximately (but not less than) $5 USD. To maintain operational feasibility, we will ensure that exchange rates are updated at regular intervals. We may also round up the disbursement amount to the nearest ZMW denomination.

9.9 Dissemination of findings

Study findings will be disseminated through appropriate local channels, including academic and public health research symposia. We will report findings to relevant local entities, including the Zambian Ministry of Health, the UNZA Biomedical Research Ethics Committee, and the National Health Research Authority. One or more publications will also be submitted to a peer-reviewed journal. Our study team plan to publish the study results whether positive or negative. The study participants' privacy and confidentiality will be strictly maintained in all results dissemination or publication activities.

10.0 TIME FRAME

Table 4: Study Time Frame

	Month								
	1	2	3	4	5	6	7	8	9
Site training	X								
Enrollment		X	X	X	X	X	X		
Follow-up visit			X	X	X	X	X	X	
Dissemination of findings									X

11.0 BUDGET

Table 5: Study Budget

Item	Cost in USD	Cost in ZMK
Operational Costs	4,144	49,446
Materials and Supplies	10,200	121,707

Field Personnel	57,100	681,317
Compensation for Participants	1,830	21,836
Total Estimated Costs	73,274	874,306

12.0 REFERENCES

1. The Joint United Nations Programme on HIV/AIDS (UNAIDS) *Fast-Track: ending the AIDS epidemic by 2030.* UNAIDS;2014.
2. Osoti A HH, Kinuthia J, Farquhar C. Role of male partners in the prevention of mother-to-child HIV transmission. *Research and Reports in Neonatology.* 2014;4:131—138.
3. Hensen B, Taoka S, Lewis JJ, Weiss HA, Hargreaves J. Systematic review of strategies to increase men's HIV-testing in sub-Saharan Africa. *AIDS (London, England).* 2014;28(14):2133-2145.
4. Wall KM, Kilembe W, Nizam A, et al. Promotion of couples' voluntary HIV counselling and testing in Lusaka, Zambia by influence network leaders and agents. *BMJ open.* 2012;2(5):e001171.
5. Conkling M, Shutes El Fau - Karita E, Karita E Fau - Chomba E, et al. Couples' voluntary counselling and testing and nevirapine use in antenatal clinics in two African capitals: a prospective cohort study. 2010(1758-2652 (Electronic)).
6. Adeola O Adeyeye MJS, David N Burns. Engaging men in HIV treatment and prevention. *The Lancet.* 2018;392:2334-2335.
7. Blackstone SR, Nwaozuru U, Iwelunmor J. Antenatal HIV Testing in Sub-Saharan Africa During the Implementation of the Millennium Development Goals: A Systematic Review Using the PEN-3 Cultural Model. *Int Q Community Health Educ.* 2018;38(2):115-128.
8. Stangl AL, Lloyd JK, Brady LM, Holland CE, Baral S. A systematic review of interventions to reduce HIV-related stigma and discrimination from 2002 to 2013: how far have we come? *Journal of the International AIDS Society.* 2013;16(3 Suppl 2):18734-18734.
9. Zanolini A, Chipungu J, Vinikoor MJ, et al. HIV Self-Testing in Lusaka Province, Zambia: Acceptability, Comprehension of Testing Instructions, and Individual Preferences for Self-Test Kit Distribution in a Population-Based Sample of Adolescents and Adults. *AIDS Research and Human Retroviruses.* 2018;34(3):254-260.
10. Joint United Nations Programme on HIV/AIDS. 2015 Progress Report on the Global Plan Towards the Elimination of New HIV Infections Among Children and Keeping Their Mothers Alive. http://www.unaids.org/en/resources/documents/2015/JC2774_2015ProgressReport_GlobalPlan. Accessed May 15, 2016.
11. Kim MH, Ahmed S, Hosseinipour MC, et al. Implementation and operational research: the impact of option B+ on the antenatal PMTCT cascade in Lilongwe, Malawi. *J Acquir Immune Defic Syndr.* 2015;68(5):e77-83.
12. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. *PLoS medicine.* 2014;11(2):e1001608.

13. Republic of Zambia Ministry of Health. Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection. In: Health Mo, ed. Zambia: Ministry of Health; 2018:1-114.
14. Mulubwa C, Hensen B, Phiri MM, et al. Community based distribution of oral HIV self-testing kits in Zambia: a cluster-randomised trial nested in four HPTN 071 (PopART) intervention communities. *The Lancet HIV.* 2018.
15. Choko AT, Kumwenda MK, Johnson CC, et al. Acceptability of woman-delivered HIV self-testing to the male partner, and additional interventions: a qualitative study of antenatal care participants in Malawi. *Journal of the International AIDS Society.* 2017;20(1):21610.
16. Kalembo FW, Zgambo M, Mulaga AN, Yukai D, Ahmed NI. Association between male partner involvement and the uptake of prevention of mother-to-child transmission of HIV (PMTCT) interventions in Mwanza district, Malawi: a retrospective cohort study. *PLoS One.* 2013;8(6):e66517.
17. Kashitala J, Nyambe N, Mwalo S, et al. Is Male Involvement in ANC and PMTCT Associated with Increased Facility-Based Obstetric Delivery in Pregnant Women? *Afr J Reprod Health.* 2015;19(2):117-124.
18. Farquhar C, Kiarie JN, Richardson BA, et al. Antenatal couple counseling increases uptake of interventions to prevent HIV-1 transmission. *J Acquir Immune Defic Syndr.* 2004;37(5):1620-1626.
19. Aluisio A, Richardson BA, Bosire R, John-Stewart G, Mbori-Ngacha D, Farquhar C. Male antenatal attendance and HIV testing are associated with decreased infant HIV infection and increased HIV-free survival. *J Acquir Immune Defic Syndr.* 2011;56(1):76-82.
20. Aluisio AR, Bosire R, Betz B, et al. Male Partner Participation in Antenatal Clinic Services is Associated with Improved HIV-free survival Among Infants in Nairobi, Kenya: A Prospective Cohort Study. *J Acquir Immune Defic Syndr.* 2016.
21. Rosenberg NE, Gross R, Mtande T, et al. "We have heard it together": a qualitative analysis of couple HIV testing and counselling recruitment in Malawi's Option B+ programme. *African journal of AIDS research : AJAR.* 2017;16(3):215-223.
22. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *The Lancet.* 2007;369(9562):643-656.
23. Aluisio A, Richardson BA, Bosire R, John-Stewart G, Mbori-Ngacha D, Farquhar C. Male antenatal attendance and HIV testing are associated with decreased infant HIV infection and increased HIV-free survival. *Journal of acquired immune deficiency syndromes (1999).* 2011;56(1):76-82.
24. Morfaw F, Mbuagbaw L, Thabane L, et al. Male involvement in prevention programs of mother to child transmission of HIV: a systematic review to identify barriers and facilitators. *Systematic reviews.* 2013;2:5-5.
25. Dovel K, Yeatman S, Watkins S, Poulin M. Men's heightened risk of AIDS-related death: the legacy of gendered HIV testing and treatment strategies. *AIDS.* 2015;29(10):1123-1125.
26. Marks G, Crepaz N Fau - Senterfitt JW, Senterfitt Jw Fau - Janssen RS, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are

infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr.* 2005(1525-4135 (Print)).
27. Bhushan NL, Golin CE, McGrath N, et al. The impact of HIV couple testing and counseling on social support among pregnant women and their partners in Lilongwe, Malawi: an observational study. *AIDS care.* 2019;31(2):199-206.
28. El-Bassel N, Gilbert L, Witte S, Wu E, Hunt T, Remien RH. Couple-based HIV prevention in the United States: advantages, gaps, and future directions. *Journal of acquired immune deficiency syndromes (1999).* 2010;55 Suppl 2(Suppl 2):S98-S101.
29. Burton J, Darbes LA, Operario D. Couples-focused behavioral interventions for prevention of HIV: systematic review of the state of evidence. *AIDS and behavior.* 2010;14(1):1-10.
30. Conkling M, Shutes EL, Karita E, et al. Couples' voluntary counselling and testing and nevirapine use in antenatal clinics in two African capitals: a prospective cohort study. *Journal of the International AIDS Society.* 2010;13:10.
31. Obermeyer CM, Osborn M. The utilization of testing and counseling for HIV: a review of the social and behavioral evidence. *Am J Public Health.* 2007;97(10):1762-1774.
32. World Health Organization (WHO). PMTCT Strategic Vision 2010-2015: preventing mother-to-child transmission of HIV to reach the UNGASS and millenium development goals. In. Geneva: WHO library Cataloguing-in-Publication Data 2010. ; 2010.
33. Sharma M, Smith JA, Farquhar C, et al. Assisted partner notification services are cost-effective for decreasing HIV burden in western Kenya. *AIDS.* 2018;32(2):233-241.
34. Wamuti BM, Erdman LK, Cherutich P, et al. Assisted partner notification services to augment HIV testing and linkage to care in Kenya: study protocol for a cluster randomized trial. *Implement Sci.* 2015;10:23.
35. World Health Organization. Guidelines on HIV self-testing and partner notification: supplement to consolidated guidelines on HIV testing services. In: HIV/AIDS, ed. Geneva: World Helath Organization 2016.
36. Nyondo AL, Choko AT, Chimwaza AF, Muula AS. Invitation Cards during Pregnancy Enhance Male Partner Involvement in Prevention of Mother to Child Transmission (PMTCT) of Human Immunodeficiency Virus (HIV) in Blantyre, Malawi: A Randomized Controlled Open Label Trial. *PloS one.* 2015;10(3):e0119273.
37. Jefferys LF, Nchimbi P, Mbezi P, Sewangi J, Theuring S. Official invitation letters to promote male partner attendance and couple voluntary HIV counselling and testing in antenatal care: an implementation study in Mbeya Region, Tanzania. *Reproductive health.* 2015;12:95.
38. Mohlala BK, Boily MC, Gregson S. The forgotten half of the equation: randomized controlled trial of a male invitation to attend couple voluntary counselling and testing. *AIDS.* 2011;25(12):1535-1541.
39. Rosenberg NE, Mtande TK, Saidi F, et al. Recruiting male partners for couple HIV testing and counselling in Malawi's option B+ programme: an unblinded randomised controlled trial. *The Lancet HIV.* 2015;2(11):e483-e491.
40. Osoti AO, John-Stewart G, Kiarie J, et al. Home visits during pregnancy enhance male partner HIV counselling and testing in Kenya: a randomized clinical trial. *AIDS.* 2014;28(1):95-103.

41. Osoti AO, John-Stewart G, Kiarie JN, et al. Home-based HIV testing for men preferred over clinic-based testing by pregnant women and their male partners, a nested cross-sectional study. *BMC Infect Dis.* 2015;15:298.
42. Krakowiak D, Kinuthia J, Osoti A, et al. Male partner home HIV testing vs. clinic invitation in pregnancy: a randomized trial. Paper presented at: 2016 Conference on Retroviruses and Opportunistic Infections 2016; Seattle, WA.
43. Krakowiak D, Kinuthia J, Osoti AO, et al. Home-Based HIV Testing Among Pregnant Couples Increases Partner Testing and Identification of Serodiscordant Partnerships. *J Acquir Immune Defic Syndr.* 2016;72 Suppl 2:S167-173.
44. Sharma M, Farquhar C, Ying R, et al. Modeling the Cost-Effectiveness of Home-Based HIV Testing and Education (HOPE) for Pregnant Women and Their Male Partners in Nyanza Province, Kenya. *J Acquir Immune Defic Syndr.* 2016;72 Suppl 2:S174-180.
45. Johnson CC, Kennedy C, Fonner V, et al. Examining the effects of HIV self-testing compared to standard HIV testing services: a systematic review and meta-analysis. *Journal of the International AIDS Society.* 2017;20(1):21594.
46. Thirumurthy H, Masters SH, Mavedzenge SN, Maman S, Omanga E, Agot K. Promoting male partner HIV testing and safer sexual decision making through secondary distribution of self-tests by HIV-negative female sex workers and women receiving antenatal and post-partum care in Kenya: a cohort study. *The Lancet HIV.* 2016;3(6):e266-e274.
47. Harichund C, Moshabela M, Kunene P, Abdool Karim Q. Acceptability of HIV self-testing among men and women in KwaZulu-Natal, South Africa. *AIDS care.* 2019;31(2):186-192.
48. Johnson C, Baggaley R, Forsythe S, et al. Realizing the potential for HIV self-testing. *AIDS and behavior.* 2014;18 Suppl 4:S391-395.
49. Gagnon M, French M, Hebert Y. The HIV self-testing debate: where do we stand? *BMC Int Health Hum Rights.* 2018;18(1):5.
50. Schaffer E, Agot K, Thirumurthy H. Role of partner violence in women's ability to distribute self-tests to male partners [Abstract #894]. Paper presented at: 2017 Conference on Retroviruses and Opportunistic Infections2017; Seattle, WA.
51. Masters SH, Agot K, Obonyo B, Napierala Mavedzenge S, Maman S, Thirumurthy H. Promoting Partner Testing and Couples Testing through Secondary Distribution of HIV Self-Tests: A Randomized Clinical Trial. *PLoS medicine.* 2016;13(11):e1002166.
52. Kaul R, Kimani J, Nagelkerke NJ, et al. Monthly antibiotic chemoprophylaxis and incidence of sexually transmitted infections and HIV-1 infection in Kenyan sex workers: a randomized controlled trial. *JAMA.* 2004;291(21):2555-2562.
53. Price MA, Rida W, Mwangome M, et al. Identifying at-risk populations in Kenya and South Africa: HIV incidence in cohorts of men who report sex with men, sex workers, and youth. *J Acquir Immune Defic Syndr.* 2012;59(2):185-193.
54. Celum C, Wald A, Hughes J, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;371(9630):2109-2119.
55. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med.* 2010;362(5):427-439.
56. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med.* 2012;367(5):399-410.

57. Chi BH, Rosenberg NE, Mweemba O, et al. Involving both parents in HIV prevention during pregnancy and breastfeeding. *Bulletin of the World Health Organization.* 2018;96(1):69-71.
58. Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care.* 2005;20(2):187-191; discussion 191-183.
59. Westreich D, Edwards JK, Lesko CR, Stuart E, Cole SR. Transportability of Trial Results Using Inverse Odds of Sampling Weights. *Am J Epidemiol.* 2017;186(8):1010-1014.
60. Buchanan AL HM, Cole SR, Mollan KR, Sax PE, Daar ES, Adimora AA, Eron JJ, Mugavero MJ. Generalizing evidence from randomized trials using inverse probability of sampling weights. *Journal of the Royal Statistical Society.* 2018;181(4):1193-1209.
61. Zhao L, Claggett B, Tian L, et al. On the restricted mean survival time curve in survival analysis. *Biometrics.* 2016;72(1):215-221.
62. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. *J Clin Oncol.* 2014;32(22):2380-2385.

13.0 APPENDICES

1. Informed Consent Forms (ICF)
    - Pre-Intervention Phase
    - Control and Intervention Arms
    - Qualitative interviews
2. Semi Structured Interview Guides
        - 1 female participants in control arm
        - 1 female participants in intervention arm
        - 1 Health Care Workers

*3.*Questionairre