

OPEN

JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000003583

The impact of a couple-based intervention on one-year viral suppression
among pregnant women living with HIV and their male partners in Malawi:

A randomized controlled trial

Running head

Impact of a couple-based intervention

Nora E. Rosenberg, PhD^{1,2§}

Lauren A. Graybill, PhD³ Tiwonge Mtande, MSocSc² Nuala McGrath,, SCd^{4,5} Suzanne Maman,
PhD, Tiyamike Nthani,, BA² Robert Krysiak, MSc² Isaac Thengolose, BA², Irving F. Hoffman,
PA^{2,6} William C. Miller, MD, PhD^{2,7} Mina Hosseinipour, MD^{2,6}

- 1 Department of Health Behavior, University of North Carolina at Chapel Hill, Chapel Hill, US
- 2 UNC Project-Malawi, University of North Carolina at Chapel Hill, Lilongwe, Malawi
- 3 Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, USA
- 4 School of Primary Care, Population Sciences and Medical Education, Faculty of Medicine, University of Southampton
- 5 Department of Social Statistics and Demography, Faculty of Social Sciences, University of Southampton, UK

- 6 Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, USA
7 Division of Epidemiology, The Ohio State University, Columbus, Ohio

§ Corresponding author:

Nora E. Rosenberg, PhD, MSPH

Department of Health Behavior

135 Dauer Drive | Rosenau Hall CB #7440 | Chapel Hill, NC 27599-7440

Gillings School of Global Public Health

University of North Carolina at Chapel Hill, Chapel Hill USA

919-966-3761 | Nora_Rosenberg@unc.edu

Conflict of interest and source of Funding: The study was supported by funding from the National Institutes of Health (R00 MH104154, R01 MH124526) with support to investigators from The UNC Center for AIDS Research. N. McGrath is a recipient of an NIHR Global Health Research Professorship award (Ref: RP-2017-08-ST2-008). We report no conflicts of interest.

Word count:

Abstract: 250/250

Main text: 3737/3500

This is an open-access article distributed under the terms of the Creative Commons

Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is

permissible to download and share the work provided it is properly cited. The work cannot

be

changed in any way or used commercially without permission from the journal.

Abstract and Key words

Introduction: Couple-based behavioral interventions (CBIs) have been associated with improved HIV virological outcomes for pregnant women and their male partners living with HIV in observational settings, but have never been tested in a randomized controlled trial (RCT).

Setting: Bwaila District Hospital Antenatal clinic (Lilongwe, Malawi).

Methods: An RCT was conducted among 500 pregnant women living with HIV (index clients) randomized 1:1 to the standard of care (SOC) or CBI and followed for one year. The CBI offered an initial session for index clients, HIV assisted partner notification, two enhanced couple counseling and testing sessions, illustrated materials, and antiretroviral therapy pick-up for either couple member at the antenatal clinic. At 12 months, viral load among index clients and male

partners with HIV was measured. Risk differences (RD) and 95% confidence intervals (CIs) compared viral suppression (<1000 copies/ml) between arms.

Results: Mean index client age was 26.6 years; most were married or cohabiting (93.3%). Index client viral suppression was 6.5% higher in the CBI arm (88.0%) than in the SOC arm (81.6%). Male partner viral suppression was 16.2% higher in the CBI arm (73.6%) than the SOC arm (57.4%). Overall couple viral suppression was 7.8% higher (CI: 0.5% to 15.1%, $p=0.04$) in the CBI arm (84%) than in the SOC arm (76.0%). Social harms were rare (3.6%) and comparable between arms ($p=0.8$).

Conclusion: This CBI had a positive impact on couple viral suppression. Scaling this CBI to antenatal clients with HIV and their male partners could improve HIV outcomes among expecting families.

NCT03477279

Keywords: HIV, testing, couple, intervention, behavior, viral load, adherence

Abstract and Key words

Introduction: Couple-based behavioral interventions (CBIs) have been associated with improved HIV virological outcomes for pregnant women and their male partners living with HIV in observational settings, but have never been tested in a randomized controlled trial (RCT).

Setting: Bwaila District Hospital Antenatal clinic (Lilongwe, Malawi).

Methods: An RCT was conducted among 500 pregnant women living with HIV (index clients) randomized 1:1 to the standard of care (SOC) or CBI and followed for one year. The CBI offered an initial session for index clients, HIV assisted partner notification, two enhanced couple counseling and testing sessions, illustrated materials, and antiretroviral therapy pick-up for either couple member at the antenatal clinic. At 12 months, viral load among index clients and male partners with HIV was measured. Risk differences (RD) and 95% confidence intervals (CIs) compared viral suppression (<1000 copies/ml) between arms.

Results: Mean index client age was 26.6 years; most were married or cohabiting (93.3%). Index client viral suppression was 6.5% higher in the CBI arm (88.0%) than in the SOC arm (81.6%). Male partner viral suppression was 16.2% higher in the CBI arm (73.6%) than the SOC arm (57.4%). Overall couple viral suppression was 7.8% higher (CI: 0.5% to 15.1%, $p=0.04$) in the CBI arm (84%) than in the SOC arm (76.0%). Social harms were rare (3.6%) and comparable between arms ($p=0.8$).

Conclusion: This CBI had a positive impact on couple viral suppression. Scaling this CBI to antenatal clients with HIV and their male partners could improve HIV outcomes among expecting families.

NCT03477279

Keywords: HIV, testing, couple, intervention, behavior, viral load, adherence

Introduction

Women of reproductive age in Africa account for approximately one-third of the 37.7 million people living with HIV globally.(1) In most African countries, pregnant and breastfeeding women living with HIV are offered immediate lifelong antiretroviral therapy (ART) through Option B+, which has treatment benefits for women and prevention benefits for infants and partners.(2) Option B+ has increased ART initiation and retention in HIV treatment programs, including in Malawi.(3) However, the region has not eliminated vertical transmission, due to challenges with maternal viral suppression across the full perinatal period.(4, 5) Furthermore, the male partners of pregnant women living with HIV experience lower levels of HIV testing and viral suppression than women.(6)

Engaging male partners in antenatal care (ANC) has benefits for women, partners, and infants.(7-9) One promising form of male engagement is couple HIV testing and counseling (CHTC), in which couple members learn their HIV status together from a counselor. CHTC has increased male partner HIV testing and disclosure, led to sexual behavior change, and improved infant outcomes, including HIV-free survival.(10-12) CHTC is often grounded in interdependence theory, the idea that behaviors can be influenced by the individual, partner, or the two together through dyadic processes such as joint communication, decision-making and goal setting.(13, 14) CHTC is typically provided once, even though most couples require ongoing testing or support. Extending CHTC to support ongoing HIV-related behaviors, especially ART adherence, could have long-term HIV treatment benefits.

Although CHTC is often available in ANC settings,(15) it remains underutilized. One approach for increasing CHTC is through HIV-assisted partner notification, in which clinic staff help recruit sexual partners exposed to HIV.(16)(17) When we pilot-tested HIV-assisted partner

notification combined with CHTC, we observed increases in male partner HIV testing and ART initiation and female one-month retention.(18) These couples described their strategies for mutual support with HIV-related behaviors.(19, 20) Based on these observations, we developed a couple-based behavioral intervention (CBI) guided by interdependence theory, integrating HIV-assisted partner notification (to recruit couples) and CHTC (to test partners and support both couple members with ART behaviors).

In this analysis, we examine the impact of this CBI on viral suppression among pregnant women living with HIV (index clients), their male partners, and both together after one year. Secondly, we examine male partner testing and social harms. We hypothesized that the CBI package would improve HIV-related outcomes compared to the standard of care (SOC).

Methods

Study setting

The study was conducted from September, 2017-August, 2020 at Bwaila Hospital in Lilongwe, Malawi. This hospital attends to ~14,000 pregnant women annually; HIV prevalence is ~10%. Women without a documented HIV status are offered opt-out HIV testing at their first antenatal care (ANC) visit. Those with an HIV-positive result are encouraged to start same-day ART.

Study design

We conducted an unmasked two-arm randomized controlled trial comparing Malawi's Option B+ SOC to a CBI. Five-hundred pregnant women with an HIV-positive HIV test result (index clients) were randomized (1:1) using permuted blocks of sizes 2, 4, and 6. The random allocation sequence was generated using SAS 9.4. Index clients were followed for one year with study visits at zero (enrollment), six, and 12 months. Male partners of index clients randomized to the

CBI arm could enroll at any point between the index client's 0- and 12-month visits, with encouragement to enroll right away. Male partners in the SOC arm could only enroll at the index client's 12-month visit; delayed enrollment avoided study procedures influencing the outcome. In both arms, index client and male partner viral suppression were assessed at 12 months. Index client perception of 1) male partner HIV status and 2) male partner testing in the last year were also reported at 12 months.

Study populations

Index clients who presented for antenatal care, tested HIV-positive, and were not already taking ART were eligible. Further eligibility characteristics included: 1) being ≥ 18 years-old or 15-17 years-old and married; 2) expecting to remain in the Bwaila catchment area for the next year or notify the study of transfers; and 3) being in an ongoing heterosexual relationship for ≥ 3 months. The male partner was someone the index was 1) willing to invite to a couple-based intervention, 2) able and willing to provide locator information for, and 3) expected to be in the catchment area for ≥ 1 week in the next six months. Additionally, index clients provided informed consent. Male partner consent was not required for index clients to enroll. Intimate partner violence (IPV) was discussed as a potential risk. Women who believed participation would lead to IPV were discouraged from consenting.

Male partners were eligible if they 1) were ≥ 18 years or 15-17 years-old and married; 2) in a relationship with the index client for ≥ 3 months; and 3) willing to receive CHTC with the index client. Male partners provided informed consent. Only one partner could be enrolled per index client, but new partners could enroll if the first relationship ended.

Study procedures

Pregnant women with a routine HIV-positive test results first provided verbal consent for eligibility screening. Eligible women who wished to participate then provided written informed consent. A research officer administered a tablet-based behavioral survey using Open Data Kit, assessing demographic and relationship characteristics, sexual and reproductive health, and IPV. Next, locator information was collected. Lastly, a research officer opened a sealed envelope and provided randomization assignment. At 6- and 12-months, the behavioral survey was repeated and index clients were asked to report social harms (i.e. challenges arising from study participation). At the 12-month visit, a plasma sample was collected for measurement of HIV viral load with GeneExpert (lower detection limit=40 copies/ μ L). For index clients randomized to CBI, intervention procedures were then conducted.

While enrollment timing differed for male partners in the SOC (12 months) and CBI arms (0-12 months), enrollment procedures were the same: verbal consent for screening, eligibility screening, and administration of informed consent. Men in the CBI arm completed the behavioral survey at 0 (0-<4), 6 (4-<10), and 12 (10-14) months following index client enrollment. They received intervention procedures at each visit. Men in the SOC arm completed the survey and were offered intervention procedures at 12 months. At the 12-month visit, men in both arms provided a venous blood sample to determine HIV status and viral load.

Index clients and male partners who failed to present to the clinic for their 12-month visit were traced and offered community-based procedures analogous to clinic-based procedures except 70 μ L dried blood spots were collected in lieu of phlebotomy. HIV RNA PCR testing was

conducted on Abbott HIV Viral Load Real Time testing with a lower detection limit of 1000 copies/ μ L. This value was used as the lower limit for all samples.

At all study visits, social harms related to study participation were assessed, as well as the nature of harm (physical, emotional, economic, social, legal) and the people involved. Study staff provided support and referrals.

SOC and CBI

Index participants received routine Option B+ procedures from facility staff (Table 1). They received TDF/3TC/EFV starting in October 2017, had the option to switch to TDF/3TC/DTG in June 2019, and were expected to switch in February 2020. At the first antenatal visit, all pregnant women were tested for HIV using group pre-test counselling, serial HIV rapid testing, and individual post-test counselling. Women could bring a sexual partner, but most did not. Referral slips were inconsistently offered to women who presented without a partner. Male partners who were HIV-positive could not obtain ART at the ANC facility; they were referred to an HIV clinic <100 meters away.

Those assigned to the CBI arm received an intervention called *Timasamalirana*, a Chichewa phrase meaning “we support each other.” *Timasamalirana* was based on formative research exploring how HIV-affected couples supported each other with ART behaviors. We incorporated these findings into an enhanced CHTC intervention focused on ART adherence. *Timasamalirana* was grounded in interdependence theory, focusing on dyadic processes, such as intra-couple communication (discussing HIV-related behaviors), joint decision-making (making decisions together about HIV-related behaviors), joint goal-setting (setting behavioral goals together), and

communal coping (supporting each other with the emotions arising from an HIV diagnosis). It comprised an index client initial visit, in which women were offered support on disclosing to and inviting partners; assisted partner notification, enhanced CHTC, an illustrated pamphlet reinforcing key messages, and the opportunity for both couple members to obtain ART at ANC. Counsellors and nurses with prior CHTC training delivered *Timasamalirana*, using checklists to guide delivery.

- *Index client initial visit (day 0-7)*: This individual session focused on coping with the diagnosis and disclosing to and inviting a male partner. Index clients received an illustrated invitation encouraging a partner to come to the clinic to receive pregnancy-related health information within one month. Procedures for phone and physical tracing were offered if their partners did not present.
- *Male partner tracing procedures (month 1-3)*: For partners who did not present after one month, phone and physical tracing began and continued for two months. The tracer followed a script reinforcing invitation messages and omitting the index client's HIV status.
- *Couple visit 1 (first 3 months)*: Couples were provided with pregnancy information, including the importance of CHTC, and offered enhanced CHTC with differentiated messages based on couple status. Messages focused on retention and ART adherence. Consistent with interdependence theory, the counselor promoted intra-couple communication and encouraged joint decision-making and joint goal-setting. Men who tested HIV-positive could initiate ART in the antenatal clinic.
- *Subsequent couple visits (month 6, 12)*: Couples received up to two follow-up sessions. Repeat testing was conducted for male partners in HIV-discordant couples. Messages on

retention and ART adherence were reinforced. Intra-couple communication, joint decision-making, and joint goal setting were revisited.

- *Ongoing procedures:* Couple members could pick up HIV treatment for themselves or one another at the ANC.

Outcomes

The primary outcome was the proportion of index clients who were HIV virally suppressed (<1000 copies/ μ l) at 12 months. The study had 83% power to detect a 10% difference in the proportion of index clients virally suppressed between arms. Among male partners living with HIV, viral suppression was the primary outcome. The study had 90% power to detect a 20% difference in the proportion of male partners virally suppressed. Viral suppression was also examined in a combined analysis among all index clients and male partners living with HIV. Secondary outcomes included partner HIV status, index client report of partner HIV status, and index client report of partner testing in the last year. Female report was used because partner testing could have occurred outside of our study, thus our observation of male partner testing was incomplete. However, male self-report of HIV testing is also provided. We also examined the number and nature of social harms.

Analysis

Index client viral suppression was analyzed using complete case and multiple imputation (MI) approaches. Complete case analysis was restricted to index clients with a 12-month viral load outcome. In the MI analysis, viral load outcomes were imputed using fully conditional specification with 50 imputed datasets. Each imputation model included our exposure and variables associated with viral suppression and study participation, such as visit attendance.

Rubin's rule was used to combine results.(21) Complete case analyses were used for all other outcomes.

For each individual-level primary and secondary outcome, a generalized linear model with an identity link and binomial distribution was used to estimate risk differences (RD) between arms and 95% confidence intervals (CI). For combined viral suppression among index clients and male partners living with HIV, a generalized estimating equation (GEE) with an identity link and binomial distribution was implemented to account for intra-couple correlation. This model included an exchangeable correlation matrix and robust variance estimators. To compare social harms, a Fisher's exact test was used.

In planned secondary analyses, we examined whether intervention dose was associated with viral suppression among index clients. We also evaluated whether the relationship between the intervention and index client viral suppression was modified by key relationship characteristics, including self-report of recent IPV at baseline. IPV was of interest, as many couple-based programs exclude such individuals. We used the revised Conflict Tactics Scale to measure IPV in the month prior to study enrollment and generated dichotomous variables for physical, sexual, and emotional violence.(22)

Ethics

This protocol was approved by Malawi's National Health Sciences Research Committee (17/03/1747) and the University of North Carolina at Chapel Hill's Institutional Review Board (17-0681) and registered at clinicaltrials.gov (NCT 03477279).

Results

Study populations

Most women screened were eligible (85.6%) (Figure 1). Primary reasons for ineligibility were not having a sexual partner at all (21.2%) or in Lilongwe (39.4%), and not being able or willing to provide partner locator information (24.8%). Among eligible women, 10.7% did not provide informed consent and 27.7% were unavailable (i.e. did not wish to remain at the clinic to complete study procedures right after their HIV diagnosis). Overall, 500 index clients were consented, enrolled, and randomized.

Mean age of index clients was 26.5 years (SD=5.4) (Table 2). Most index clients (71%) enrolled in their second trimester; 20% were primigravida. Most (90%) had been tested for HIV, though few (8%) had received an HIV-positive test result. Nearly all index clients reported being married or cohabitating with their partner (93%); median relationship length was 2.1 years (interquartile range: 1-6 years). Some women reported emotional (18%), physical (7%), or sexual (11%) IPV in the last month with their expected study partner. Only 16% of index clients presented to their initial ANC visit with a partner.

Overall, 72.6% of index clients completed a six-month visit and 81.0% completed a 12-month visit. Retention was similar between CBI and SOC at six (73.2% vs. 72.0%, $p=0.8$) and 12 months (80.8% vs. 81.2%, $p=0.9$) (Appendix 1). Younger and primigravida women were less likely to have a 12-month visit.

About half of index clients ($n=264$, 52.8%) had a male partner who consented and enrolled. Male partner participation differed by arm (CBI: 166/250; SOC: 98/250). Mean partner age was 33.2 years (SD=7.0). Two women in the CBI arm had two partners enroll over the course of 12 months. Of 236 partners who never presented, 53.8% were not locatable, 28.0% had

relationships that ended, 16.1% were not interested, and 2.2% died. Challenges locating partners were due to difficulties finding addresses, address changes, and absences at the time of tracing.

CBI engagement

In the CBI arm, 143 (57.2%) couples had an initial couple visit (0-4 months) and 92 (36.8%) had a six-month visit (5-8 months). Ninety-nine CBI couples (39.6%) did not have any couple visits, 70 couples (28.0%) had one visit, and 81 (32.4%) had two visits. Couples' first visit involved both partners testing (24%), only the male partner testing (44%) and neither partner testing (31%). All included counseling.

Viral suppression outcomes

In complete case analysis, there was a trend towards higher 12-month index client viral suppression in the CBI arm (88.0% vs. 81.6%; RD: 6.5%, CI: -0.9%, 13.8%, $p=0.08$). Risk differences were similar in MI analysis, though point estimates were lower (81.1% vs. 74.2% RD: 6.9%, CI: -1.8%, 15.6). Women in the CBI arm who received two couple counselling sessions ($n=81$) were more likely to be virally suppressed than women in the SOC arm (91.4% vs. 81.6%; RD: 9.8%, CI: 1.4%, 18.1%, $p=0.02$). Adherence levels were 86.8% and 84.0% for those with zero and one session, respectively.

Imprecise trends were suggestive of effect measure modification by relationship characteristics. The CBI had a positive effect among those who did *not* experience recent physical IPV (RD: 7.9%, 95% CI: 0.2%, 15.5%), but not among those with recent physical IPV (RD: -9.6%, -41.6%, 22.3%) (Figure 2). The CBI also had a positive effect among women who reported being married or cohabitating and those in a relationship for at least one year.

More partners had a 12-month visit in the CBI arm than the SOC arm (54.4% vs 39.2%, $p<0.01$). Among men who presented at 12 months, nearly all (98.3%) were tested for HIV. The proportion of men who tested HIV-positive was comparable between arms (52.9% vs. 55.1%, $p=0.7$). Among men living with HIV, viral suppression was more common in the CBI arm (73.6% vs. 57.4%; RD: 16.2%, CI: -0.5%, 32.9%, $p=0.06$).

Examining index clients and male partners together, viral suppression was more common in the CBI arm (84.0% vs. 76.0%, RD: 7.8%, CI: 0.5%, 15.1%, $p=0.04$).

Secondary Outcomes

At 12 months, women in the CBI arm were more likely to report knowing their partner's HIV status (82.2% vs. 71.8%; RD: 10.3%, CI: 1.8%, 18.9%, $p=0.02$) and that their partner had HIV testing in the last year (72.2% vs. 57.1%; RD: 15.1%, CI: 4.7%, 25.5%, $p=0.05$) (Table 3).

Social Harms

Eighteen social harms were reported with similar frequency across arms ($p=0.8$). Most (78%) involved family or people in the home (typically the partner); the rest involved friends. Most were emotional (83%) or financial (28%); two were physical (11%). One woman in the CBI arm was assaulted by her partner because he was angered by study participation. She was referred for medical and psychosocial support and elected to remain in the study.

Discussion

Our trial evaluated the impact of a CBI on viral suppression among pregnant women living with HIV and their male partners one year after HIV testing. The CBI improved viral suppression at

12 months when both partners were considered together. When men and women were considered separately, improvements in viral suppression were observed, though not statistically significant.

Within ANC, couple-based interventions improve male partner HIV testing, vertical transmission, maternal ART initiation, and condom use, but the impact on female and male partner viral suppression had not been assessed previously.(9, 10, 23, 24) Male engagement, such as HIV status disclosure, clinic attendance, and co-enrollment in care, is associated with maternal retention, treatment adherence, and viral suppression in observational studies.(25-30)

Our study is the first randomized assessment of a couple-based intervention on viral suppression in an African setting. It is also one of the first to show an impact on maternal or male partner cascade outcomes.(31-33) One key study examined Mozambican pregnant women living with HIV and their male partners. An intensive multi-session CBI had no effect on ART refills for women and only a small effect on ART refills for men.(33) Our stronger effects are likely due to a different comparison group. Our comparison group was a cohort of individual women, whereas the Mozambican comparison group was a cohort of couples who were aware of each other's status. This suggests that the simple act of bringing couples together may be more impactful than ongoing counseling.

Timasamalirana integrates HIV assisted partner notification with enhanced CHTC. In traditional HIV assisted partner notification, partners are contacted anonymously, a practice that protects the identity of the index, but often misses benefits for couples. Drawing on interdependence theory, we engaged partners as collaborators who could provide and benefit from the index client's support.(20, 34) Facilitating couple engagement, interdependence, and couple communication stands in contrast to many partner notification interventions, which offer counselling to couple

members separately.(28) Our formative work, which unearthed existing forms of support,(19) was integrated into *Timasamalirana*. Interdependence theory has been incorporated into similar ongoing trials in SSA, with results forthcoming (35, 36) and impactful studies in the US.(37)

Couple-based behavioral interventions are appropriate for many, but not all pregnant women with HIV. We excluded women who did not wish to engage in a couple-based intervention, did not have a partner, or did not believe their partner would be available. Some eligible women declined to provide consent due to the nature of the intervention. Together, these groups represented approximately one quarter of the women that we screened. Additionally, some women did not have time or interest to participate in a study on the day of their HIV diagnosis. Furthermore, women in the CBI arm who were in shorter, non-marital relationships and violent partnerships did not exhibit higher levels of viral suppression. These findings are comparable to a South African study which found HIV status disclosure associated with viral suppression only among women in married/cohabiting relationships.(25) Based on the lack of effectiveness and the potential for harm, restricting couple-based interventions to couples without recent physical intimate partner violence is advised and the current standard in Malawi's index case testing program. Different interventions, or a different type of supporter, may help women experiencing IPV, a population in need of support.(38)

Timasamalirana is one type of treatment-supporter intervention, a program that leverages social support to achieve HIV outcomes. Treatment supporters, especially those selected by the patient, also positively impact viral suppression in similar settings.(39-41) Such interventions are promising as they require minimal resources and often offer daily support. Although adults on ART in Malawi identify a treatment supporter their role is often limited to medication pickup. Our intervention substantially expanded the nature, interactivity, and scope of this role.

Our intervention holds promise for scale-up, given its impact on multiple outcomes of interest to UNAIDS and national HIV programs. Our intervention required only one individual counselling session, assisted partner notification, and two CHTC sessions that could be aligned with other antenatal and infant milestones. Furthermore, individual components are already part of many national programs.

Study procedures were intentionally minimal. Index client study visits were spaced six months apart to prevent study retention from influencing clinical retention. One consequence of this decision was index client loss to follow-up, a limitation. To address this limitation, we observed retention was similar between arms; additionally MI and complete-case findings were similar, suggesting results were not driven by differential follow-up.

Male participation in the intervention and trial were lower than expected, another set of limitations (6, 28). Only 60% of men participated in the counseling sessions. Nonetheless, the intervention improved male partner HIV testing from a baseline of 16%. Sub-optimal participation was due, in part, to contextual factors, including long-distance relationships, challenges finding physical locations, and relationship dissolution. As a result, power to detect a difference in viral suppression was reduced. In spite of moderate participation, we observed a difference in viral suppression between arms, suggesting resilience to imperfect implementation.

We do not report on vertical HIV transmission due to difficulties linking maternal and infant records or on sexual transmission due to the relatively small sample size. These omissions are another limitation. However, viral suppression is known to reduce both vertical and sexual transmission, and we would expect these downstream benefits.(42, 43)

Despite a decade of Option B+ scale-up, most African countries have not eliminated HIV vertical transmission, nor achieved adult 95-95-95 UNAIDS targets. *Timasamalirana*, a simple and scalable intervention, could impact both sets of targets if brought to scale.

ACCEPTED

Acknowledgements

We would like to thank the 500 families who participated our study, the study and Bwaila staff, and the Lilongwe District Health Office.

Authors' contributions

NER conceptualized and designed the study with mentorship from NM, SM, RK, IH, WCM, and MH. TM and TN oversaw data collection. NER and LAG verified the underlying data. LAG analyzed the data and oversaw the development of tables and figures. RK and IT oversaw laboratory assays. All authors reviewed and edited the manuscript and approved the final submission.

References

1. UNAIDS. UNAIDS Data 2021. Geneva: Joint United Nations Programme on HIV/AIDS; 2022. p. 468.
2. Schouten EJ, Jahn A, Midiani D, Makombe SD, Mnthambala A, Chirwa Z, et al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. *Lancet*. 2011;378(9787):282-4.
3. Haas AD, Msukwa MT, Egger M, Tenthani L, Tweya H, Jahn A, et al. Adherence to Antiretroviral Therapy During and After Pregnancy: Cohort Study on Women Receiving Care in Malawi's Option B+ Program. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2016;63(9):1227-35.
4. Knettel BA, Cichowitz C, Ngocho JS, Knippler ET, Chumba LN, Mmbaga BT, et al. Retention in HIV Care During Pregnancy and the Postpartum Period in the Option B+ Era: Systematic Review and Meta-Analysis of Studies in Africa. *Journal of acquired immune deficiency syndromes*. 2018;77(5):427-38.
5. Chi BH, Mbori-Ngacha D, Essajee S, Mofenson LM, Tsiouris F, Mahy M, et al. Accelerating progress towards the elimination of mother-to-child transmission of HIV: a narrative review. *Journal of the International AIDS Society*. 2020;23(8):e25571.
6. Stannah J, Soni N, Lam JKS, Giguere K, Mitchell KM, Kronfli N, et al. Trends in HIV testing, the treatment cascade, and HIV incidence among men who have sex with men in Africa: a systematic review and meta-analysis. *The lancet HIV*. 2023;10(8):e528-e42.

7. Aluisio AR, Bosire R, Bourke B, Gatuguta A, Kiarie JN, Nduati R, 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. *Journal of acquired immune deficiency syndromes*. 2016;73(2):169-76.
8. Brusamento S, Ghanotakis E, Tudor Car L, van-Velthoven MH, Majeed A, Car J. Male involvement for increasing the effectiveness of prevention of mother-to-child HIV transmission (PMTCT) programmes. *Cochrane database of systematic reviews*. 2012;10:CD009468.
9. Audet CM, Blevins M, Chire YM, Aliyu MH, Vaz LM, Antonio E, et al. Engagement of Men in Antenatal Care Services: Increased HIV Testing and Treatment Uptake in a Community Participatory Action Program in Mozambique. *AIDS and behavior*. 2016;20(9):2090-100.
10. Hampanda K, Pelowich K, Chi BH, Darbes LA, Turan JM, Mutale W, et al. A Systematic Review of Behavioral Couples-Based Interventions Targeting Prevention of Mother-to-Child Transmission in Low- and Middle-Income Countries. *AIDS and behavior*. 2022;26(2):443-56.
11. World_Health_Organization. Couples HIV Testing and Counseling Including Antiretroviral Therapy for Treatment and Prevention in Serodiscordant Couples: Recommendations for a Public Health Approach. 2012.
12. Kennedy CE, Medley AM, Sweat MD, O'Reilly KR. Behavioural interventions for HIV positive prevention in developing countries: a systematic review and meta-analysis. *Bulletin of the World Health Organization*. 2010;88(8):615-23.

13. Karney BR, Hops H, Redding CA, Reis HT, Rothman AJ, Simpson JA. A framework for incorporating dyads in models of HIV-prevention. *AIDS and behavior*. 2010;14(Suppl 2):189-203.
14. Lewis MA, McBride CM, Pollak KI, Puleo E, Butterfield RM, Emmons KM. Understanding health behavior change among couples: an interdependence and communal coping approach. *Social science & medicine*. 2006;62(6):1369-80.
15. Hampanda KM, Pelowich K, Freeborn K, Graybill LA, Mutale W, Jones KR, et al. Strategies to increase couples HIV testing and counselling in sub-Saharan Africa: a systematic review. *Journal of the International AIDS Society*. 2023;26(3):e26075.
16. World_Health_Organization. Guidelines on HIV self-testing and partner notification: supplement to consolidated guidelines on HIV Testing Services. Geneva, Switzerland: WHO Press; December 2016.
17. Osoi AO, John-Stewart G, Kiarie J, Richardson B, Kinuthia J, Krakowiak D, 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.
18. Rosenberg NE, Mtande TK, Saidi F, Stanley C, Jere E, Paile L, 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):e483-91.
19. Rosenberg NE, Gross R, Mtande T, Maman S, Golin CE, Saidi F, 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):215-23.

20. Bhushan NL, Golin CE, McGrath N, Maman S, Tsidya M, Chimndozi L, 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.
21. Rubin DB. *Multiple imputation for nonresponse in surveys*. New York, NY: Wiley; 1987.
22. Chapman H, Gillespie SM. The revised conflict tactics scales (CTS2): a review of the properties, reliability, and validity of the CTS2 as a measure of partner abuse in community and clinical samples. *Aggression Violent Behavior*. 2019;44:27-35.
23. 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.
24. LaCroix JM, Pellowski JA, Lennon CA, Johnson BT. Behavioural interventions to reduce sexual risk for HIV in heterosexual couples: a meta-analysis. *Sexually transmitted infections*. 2013;89(8):620-7.
25. Brittain K, Mellins CA, Remien RH, Phillips TK, Zerbe A, Abrams EJ, et al. Impact of HIV-Status Disclosure on HIV Viral Load in Pregnant and Postpartum Women on Antiretroviral Therapy. *Journal of acquired immune deficiency syndromes*. 2019;81(4):379-86.
26. Gill MM, Hoffman HJ, Bobrow EA, Mugwaneza P, Ndatimana D, Ndayisaba GF, et al. Detectable Viral Load in Late Pregnancy among Women in the Rwanda Option B+ PMTCT Program: Enrollment Results from the Kabeho Study. *PloS one*. 2016;11(12):e0168671.
27. Myer L, Abrams EJ, Zhang Y, Duong J, El-Sadr WM, Carter RJ. Family matters: Co-enrollment of family members into care is associated with improved outcomes for HIV-infected

women initiating antiretroviral therapy. *Journal of acquired immune deficiency syndromes*. 2014;67 Suppl 4:S243-9.

28. Jones DL, Rodriguez VJ, Soni Parrish M, Kyoung Lee T, Weiss SM, Ramlagan S, et al. Maternal and infant antiretroviral therapy adherence among women living with HIV in rural South Africa: a cluster randomised trial of the role of male partner participation on adherence and PMTCT uptake. *SAHARA J : journal of Social Aspects of HIV/AIDS Research Alliance / SAHARA* , Human Sciences Research Council. 2021;18(1):17-25.

29. van Lettow M, Cataldo F, Landes M, Kasende F, Nkhoma P, van Oosterhout JJ, et al. Impact of inter-partner HIV disclosure patterns in Malawi's PMTCT program: A mixed-method study. *PloS one*. 2019;14(7):e0219967.

30. Beyene GA, Dadi LS, Mogas SB. Determinants of HIV infection among children born to mothers on prevention of mother to child transmission program of HIV in Addis Ababa, Ethiopia: a case control study. *BMC infectious diseases*. 2018;18(1):327.

31. Puchalski Ritchie LM, van Lettow M, Pham B, Straus SE, Hosseinipour MC, Rosenberg NE, et al. What interventions are effective in improving uptake and retention of HIV-positive pregnant and breastfeeding women and their infants in prevention of mother to child transmission care programmes in low-income and middle-income countries? A systematic review and meta-analysis. *BMJ open*. 2019;9(7):e024907.

32. Vrazo AC, Firth J, Amzel A, Sedillo R, Ryan J, Phelps BR. Interventions to significantly improve service uptake and retention of HIV-positive pregnant women and HIV-exposed infants along the prevention of mother-to-child transmission continuum of care: systematic review. *Tropical medicine & international health : TM & IH*. 2018;23(2):136-48.

33. Audet CM, Graves E, Shepherd BE, Prigmore HL, Brooks HL, Emilio A, et al. Partner-Based HIV Treatment for Seroconcordant Couples Attending Antenatal and Postnatal Care in Rural Mozambique: A Cluster Randomized Controlled Trial. *Journal of acquired immune deficiency syndromes*. 2024;96(3):259-69.
34. Rosenberg NE, Graybill LA, Wesevich A, McGrath N, Golin CE, Maman S, et al. The Impact of Couple HIV Testing and Counseling on Consistent Condom Use among Pregnant Women and their Male Partners: An Observational Study. *Journal of acquired immune deficiency syndromes*. 2017.
35. Kwena Z, Kimbo L, Darbes LA, Hatcher AM, Helova A, Owino G, et al. Testing strategies for couple engagement in prevention of mother-to-child transmission of HIV and family health in Kenya: study protocol for a randomized controlled trial. *Trials*. 2021;22(1):19.
36. Hampanda K, Matenga TFL, Nkwemu S, Shankalala P, Chi BH, Darbes LA, et al. Designing a couple-based relationship strengthening and health enhancing intervention for pregnant women living with HIV and their male partners in Zambia: Interview findings from the target community. *Social science & medicine*. 2021;283:114029.
37. 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*. 2010;55 Suppl 2:S98-101.
38. Hatcher AM, Brittain K, Phillips TK, Zerbe A, Abrams EJ, Myer L. Longitudinal association between intimate partner violence and viral suppression during pregnancy and postpartum in South African women. *Aids*. 2021;35(5):791-9.

39. Nyoni T, Sallah YH, Okumu M, Byansi W, Lipsey K, Small E. The effectiveness of treatment supporter interventions in antiretroviral treatment adherence in sub-Saharan Africa: a systematic review and meta-Analysis. *AIDS care*. 2020;32(Suppl 2):214-27.
40. Kanters S, Park JJ, Chan K, Socias ME, Ford N, Forrest JJ, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *The lancet HIV*. 2017;4(1):e31-e40.
41. Dave S, Peter T, Fogarty C, Karatzas N, Belinsky N, Pant Pai N. Which community-based HIV initiatives are effective in achieving UNAIDS 90-90-90 targets? A systematic review and meta-analysis of evidence (2007-2018). *PloS one*. 2019;14(7):e0219826.
42. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *The New England journal of medicine*. 2011;365(6):493-505.
43. Tippett Barr BA, van Lettow M, van Oosterhout JJ, Landes M, Shiraishi RW, Amene E, et al. National estimates and risk factors associated with early mother-to-child transmission of HIV after implementation of option B+: a cross-sectional analysis. *The lancet HIV*. 2018;5(12):e688-e95.

Figure legends

Figure 1: Consort diagram

This figure displays the consort diagram for the *Timasamalirana* trial.

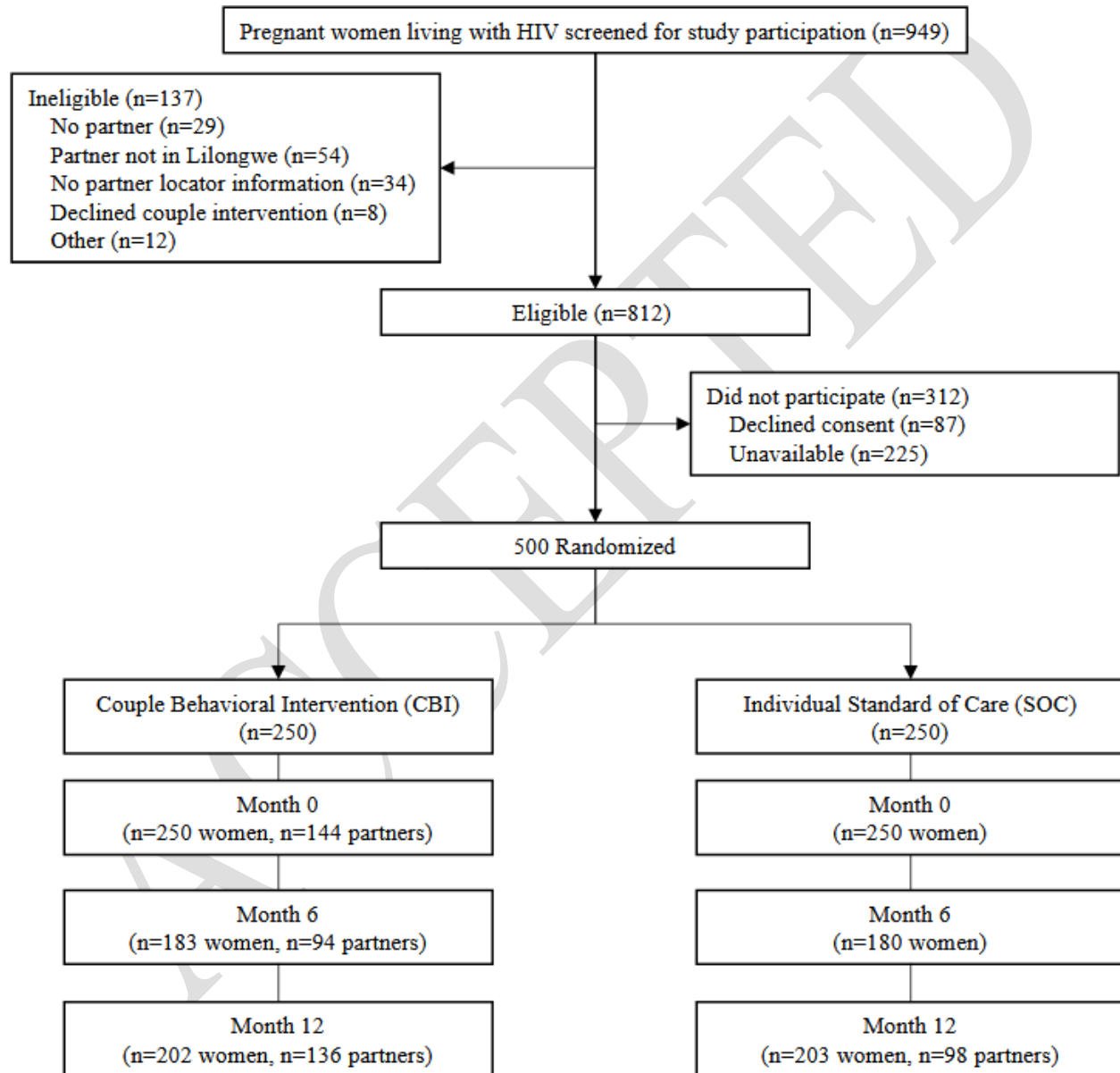


Figure 2: Index client, partner, and couple viral suppression at 12 months

This figure compares viral suppression for the CBI and SOC.

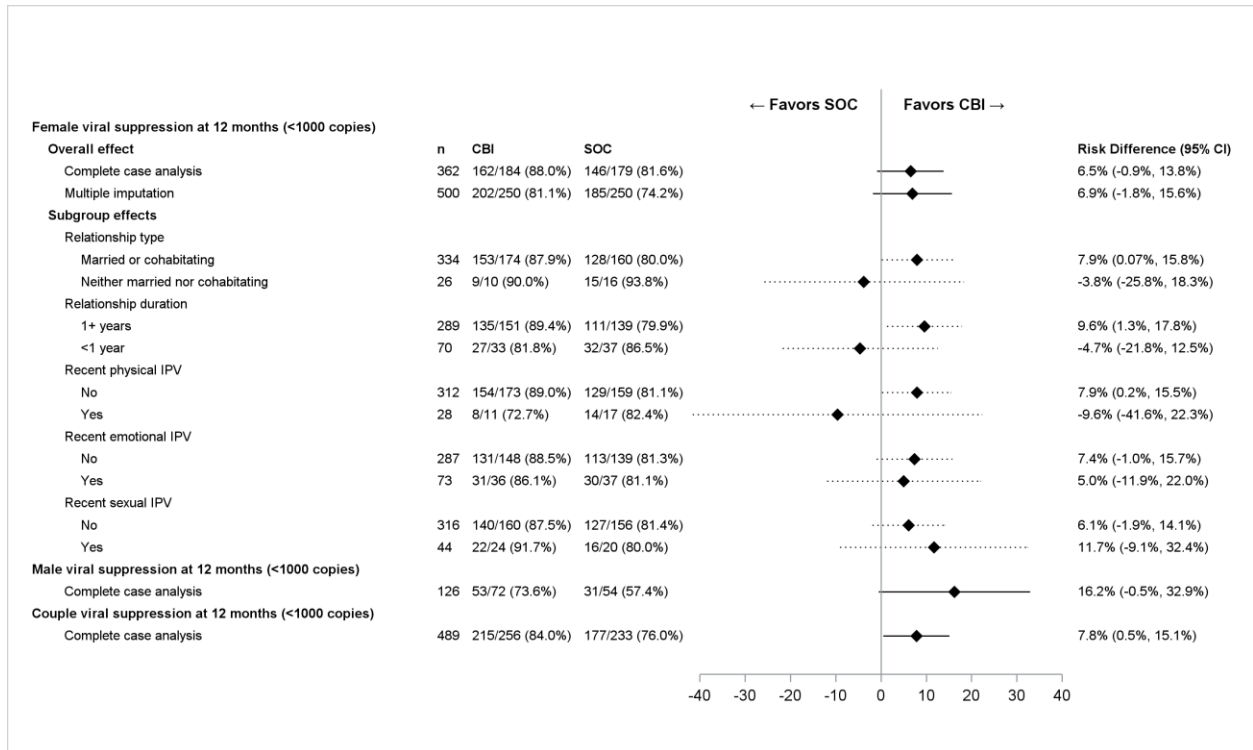


Table 1. Comparison of CBI and SOC procedures

	CBI	SOC
Initial visit (day 0-7)		
HIV testing during antenatal care (individual or couple testing available)	✓	✓
Distribution of family referral slip to invite male partner for testing	✓	✓
Counselling on disclosure and partner recruitment	✓	
Partner invitation for pregnancy information	✓	
Partner recruitment (first three months)		
Phone and physical tracing if couple does not present	✓	
Couple visit 1 (first three months)		
Enhanced couple counselling and testing <ul style="list-style-type: none"> Joint goal-setting, problem-solving, couple communication around treatment, prevention, and PMTCT behaviors 	✓	
Male partner ART initiation in ANC setting	✓	
Illustrated materials reinforcing pregnancy and HIV messages	✓	
Couple visit 2 (6 months)		
Enhanced couple counselling and testing <ul style="list-style-type: none"> Joint goal-setting, problem-solving, couple communication 	✓	

around treatment, prevention, and PMTCT behaviors		
Ongoing		
Either couple member could pick up pills for partner or themselves	✓	
Final couple visit (12 months)		
Phone and physical tracing	✓	✓
Enhanced couple counselling and testing <ul style="list-style-type: none"> • Joint goal-setting, problem-solving, couple communication around treatment, prevention, and PMTCT behaviors 	✓	✓
Illustrated materials reinforcing HIV messages	✓	✓

ACCEPTED

Table 2. Baseline characteristics of female participants

		CBI (n=250)	SOC (n=250)
Age	< 20 years	24 (10%)	27 (11%)
	20-24 years	73 (29%)	77 (31%)
	25-29 years	75 (30%)	71 (29%)
	≥ 30 years	77 (31%)	71 (29%)
Educational attainment	Did not complete primary school	109 (44%)	100 (41%)
	Primary school complete	108 (43%)	106 (43%)
	Secondary school complete	32 (13%)	40 (16%)
Estimated gestational age	1-3 Months	29 (13%)	25 (12%)
	4-6 Months	155 (70%)	156 (72%)
	≥ 7 Months	39 (17%)	35 (16%)

		CBI	SOC
		(n=250)	(n=250)
Number of past pregnancies	0 prior pregnancies	50 (20%)	48 (20%)
	1 prior pregnancy	49 (20%)	66 (27%)
	≥ 2 prior pregnancies	150 (60%)	132 (54%)
Most recent HIV test result	Never tested	23 (9%)	28 (11%)
	HIV negative	202 (81%)	195 (80%)
	HIV positive	21 (8%)	19 (8%)
	HIV indeterminate	3 (1%)	3 (1%)
Partners in last 6 months	0 sex partners	2 (1%)	0 (0%)
	1 sex partner	233 (94%)	238 (97%)

		CBI	SOC
		(n=250)	(n=250)
	≥ 2 sex partners	13 (5%)	7 (3%)
Marital status	Not married or cohabitating	14 (6%)	19 (8%)
	Married or cohabitating	235 (94%)	227 (92%)
Length of relationship	< 1 year	49 (20%)	53 (22%)
	1-4 years	112 (45%)	125 (51%)
	5-9 years	48 (19%)	34 (14%)
	≥ 10 years	39 (16%)	33 (13%)
Partner age difference	Male partner < 5 years older	80 (36%)	93 (43%)
	Male partner 5-9 years older	66 (30%)	62 (29%)
	Male partner ≥ 10 years older	36 (16%)	33 (15%)
	Does not know partner age	40 (18%)	29 (13%)

		CBI	SOC
		(n=250)	(n=250)
Primary partner HIV status	HIV negative	117 (47%)	100 (41%)
	HIV positive	28 (11%)	25 (10%)
	HIV indeterminate	2 (1%)	0 (0%)
	HIV status unknown	102 (41%)	121 (49%)
Past couple testing	Yes	79 (32%)	68 (28%)
	No	168 (68%)	177 (72%)
Emotional IPV in past 30 days	Yes	46 (18%)	45 (18%)
	No	203 (82%)	201 (82%)

		CBI	SOC
		(n=250)	(n=250)
Physical IPV in past 30 days	Yes	13 (5%)	23 (9%)
	No	236 (95%)	223 (91%)
Sexual IPV in past 30 days	Yes	28 (11%)	28 (11%)
	No	221 (89%)	218 (89%)

Column totals may not sum to 250 due to missing data

Table 3• Male partner outcomes at 12 months

	<u>CBI</u>	<u>SOC</u>	
	n/N (%)	n/N (%)	RI
<u>Male outcomes</u>			
	(82.2%	130/18 (71.8%	
Female aware of primary partner HIV status at 12 months	152/185)	1)	10.3%
Female report of primary partner HIV testing in past 12	(72.2%	(57.1%	
months	117/162)	88/154)	15.1%
	(80.4%	(68.1%	
<u>Male report of HIV testing in the past 12 months</u>	82/102)	47/69)	12.3%
<u>Male outcomes (ascertained from male partner's blood sample)</u>			
Male partner HIV status			
	(28.8%	(21.6%	
HIV positive	72)	54)	
	(25.2%	(16.4%	
HIV negative	63)	41)	
Refused testing	1 (0.4%)	3 (1.2%)	

Not observed

(45.6%
114)

(60.8%
152)

ACCEPTED