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Integration of a Relationship-focused Counseling Intervention with Delivery of the Dapivirine Ring for HIV Prevention to Women in Johannesburg: Results of the CHARISMA Pilot Study

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Abstract

Biomedical, female-initiated HIV prevention methods can help reduce disproportionately high HIV rates among women in sub-Saharan Africa, but male partner resistance and intimate partner violence (IPV) may impact ability to ensure effective use. To support consistent use of the dapivirine vaginal ring (VR), we pilot-tested the impact of the CHARISMA relationship counseling intervention ("CHARISMA") with women enrolled in the multi-site open-label Microbicide Trials Network (MTN) 025/HOPE trial at the Wits Reproductive Health and HIV Research Institute (Wits RHI) site in Johannesburg, South Africa. Lay counselors used a 42-item tool with five subscales to assess relationships and IPV and provide tailored counseling at enrolment, followed by a booster counselling session at Month 1 and follow-up checks at Months 3 and 6. We evaluated potential impact by examining self-reported ring disclosure to partners, partner clinic attendance, self-reported incident social harms (SH) and IPV, and biomarkers of ring adherence at Wits RHI. We subsequently compared these outcomes at three comparator HOPE study sites using multivariable regression models. Comparator study sites were purposively selected as those most similar to Wits RHI for baseline characteristics identified a priori. At Wits RHI, 95 of 96 (99%) HOPE participants enrolled into the CHARISMA pilot study. Mean age was 30, 36.8% lived with a partner, and 85.3% received their partner's financial support. During the six months of pilot study follow-up, participants reported: ring use disclosure to partners at 72.7%

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Conflict of interest The authors have no conflicts of interest to disclose.

Ethical approval The study was approved by the Institutional Review Boards at RTI International, all study sites, and was overseen by the regulatory infrastructure of the US National Institutes of Health and the Microbicide Trials Network.

Consent to participate All study participants provided written informed consent to participate in the study through a consent process approved by local ethical review committees in all research settings.

Consent for publication All participants were informed that any publication of this study will not use their name or identify them personally.

visits; 4.3% partners attending the research clinic; one partner-related SH; and 9.5% experienced incident IPV. The mean level of dapivirine released from returned used rings was 3.4 mg (SD 1.56), suggesting moderate adherence. Participants in the CHARISMA pilot had high background prevalence and incidence of IPV but were nevertheless able to adhere to ring use, and some male partners came to the research clinic. In adjusted regression models, compared to Wits RHI, partner clinic attendance was lower at all comparator sites; and significantly so at Site A (aRR 0.12, 95% CI 0.00–0.98). Sites B and C had lower levels of dapivirine released (suggesting lower adherence), but this difference was not significant. Site B women were more likely to report ring disclosure to partners at FU visits (aRR 1.12, 95% CI 1.00–1.25). IPV reported during follow-up was significantly lower at Site B (aRR 0.20, 95% CI 0.04–0.98, p = 0.047). CHARISMA taught women skills to decide on levels of ring-use disclosure to partners or others; therefore it is difficult to interpret differences in ring disclosure to partners with other sites. Similarly, CHARISMA heightened participants' awareness of abuse, possibly increasing IPV reports. Testing CHARISMA under fully-powered controlled conditions will improve understanding of its impact on women's relationships and ability to use female-initiated HIV prevention methods.

Keywords

IPV; Male engagement; Ring; South Africa

Background

HIV acquisition in women living in sub-Saharan Africa remains a pervasive and dominant feature of the global HIV epidemic [1]. Two important reasons for the disproportionate burden in this population include women's inability to successfully use HIV prevention methods because of social factors, including those related to IPV and gender inequity in their relationships, and the relative dearth of prevention products that women can initiate and control themselves [2–6].

The dapivirine vaginal ring is a promising female-initiated biomedical HIV prevention method that has just received a positive opinion from the European Medicines Agency (EMA), the first step for its regulatory approval in HIV-endemic countries [7]. Two Phase III studies, the International Partnership for Microbicides (IPM) 027/The Ring Study and Microbicide Trials Network (MTN)-020/ ASPIRE Study, reported that the monthly dapivirine ring reduced the overall risk of HIV-1 infection in women by 35% and 27%, respectively, and was well-tolerated with long-term use[8–10]. In both studies, participants had suboptimal ring adherence. Some participants in the ASPIRE study reported in qualitative interviews that they used rings inconsistently because they feared that the ring would be discovered during sex, instigate relationship problems among those that had not disclosed study participation, or be otherwise disruptive during sex or disfavored by partners [11]. Women experiencing social harms during ASPIRE, and those with unsupportive male partners had lower ring adherence in controlled models [6, 12]. Following these trials, the open label extension (OLE) studies of the dapivirine ring, called IPM 032/DREAM (Dapivirine Ring Extended Access and Monitoring) and MTN-025/ HOPE (HIV Open-label Prevention Extension), were implemented to assess extended safety and adherence. HOPE

results indicated high uptake and use of the ring across sites, but adherence remained suboptimal for some, even in the context of open label use of a product of known efficacy [13].

Strategies to mitigate barriers to dapivirine ring adherence that are exacerbated by negative partner dynamics and unhealthy or violent relationships could improve this product's effectiveness and public health impact. We conducted a pilot study of the CHARISMA relationship counseling intervention, which was integrated into the Wits RHI Johannesburg site of the HOPE study [14]. The CHARISMA pilot aimed to measure acceptability and feasibility of the intervention, reported elsewhere [15], and to assess its preliminary impact on three goals: improve partner communication and support through ring-use disclosure and clinic engagement; decrease social harms (SHs) and IPV; and increase ring use. Results of the latter component of the CHARISMA pilot study are presented here, with a discussion of recommended next steps.

Methods

Parent Study

HOPE (ClinicalTrials.gov: NCT02858037) was a multi-site, open-label, randomized, Phase 3B trial of the dapivirine vaginal ring conducted between July 2016 and October 2018 at 14 trial sites in South Africa, Malawi, Uganda and Zimbabwe. HOPE participants were offered the Dapivirine Vaginal Ring, a silicone elastomer vaginal ring containing 25 mg of dapivirine, to be replaced monthly, for a total period of 12 months of use. Study participants were recruited from the ASPIRE trial, a Phase III study which aimed at determining whether a vaginal ring containing the ARV drug dapivirine was a safe and effective method for protecting against the sexual transmission of HIV [9]. The HOPE sample size was contingent upon how many former ASPIRE participants were interested in enrolling, were HIV-negative, and otherwise eligible to enroll. Women who enrolled in HOPE could choose, at any time, not to use or not to accept the ring being offered. Study follow-up visits occurred monthly for the first 3 months; for the remaining 9 months, women could choose to come back to the clinic monthly to pick up a new ring each month or quarterly and take 3 rings at a time, reflecting a transition to a more real-world type of follow-up (versus a clinical trial approach). At each HOPE visit, study participants received adherence counseling aimed to support whichever HIV prevention approach they selected, including any partner-related issues such as IPV or ring non-disclosure of ring that may have come up [16].

Population and Setting

All 96 women enrolling into HOPE from December 2016 through 16 Nov 2017 at the Wits RHI site in Johannesburg, South Africa, were invited at their enrollment visit to participate in the CHARISMA pilot study.

Intervention Description

CHARISMA was implemented by lay counselors who had previous experience in HIV counseling and testing and couples counseling. They received five days of training

on gender and violence, sexual relationship dynamics, empowerment counseling skills, and understanding the specific CHARISMA counseling modules and approach. The CHARISMA intervention included empowerment counseling implemented at enrollment, a shorter booster session at the Month 1 HOPE visit, and ongoing follow-up with counseling as needed through their month 3 and 6 HOPE visits. Intervention details are described in brief below, with more information about development and specific content published elsewhere [14, 15].

During the enrollment session, the lay counselors screened participants using a tool called the HEAlthy Relationship assessment Tool (HEART), which assessed the quality of participants' relationship(s) with their male partner(s) and potential barriers or facilitators to use of HIV prevention products. The lay counselors then provided skills-based, interactive counseling using a modified version of the Safe & Sound IPV intervention adapted to a non-pregnant population [17]. CHARISMA counseling included a brief module on healthy relationships and a module on either partner communication (A), ring disclosure (B), or responding to IPV (C), based on the HEART and the counselor's assessment of their needs. In general, assignment of a counseling module was hierarchical. If a participant reported any violence in the relationship, she was administered the module on responding to IPV (C), which included content around the cycle of violence, safety planning, and other access to other referral resources. If there was no violence, but the participant expressed that she had not disclosed ring use to her partner, or had challenges with disclosure, she was offered the module on ring disclosure (B). The disclosure module also helped women decide whether they could safely disclose ring use to their partners (vs. promoting disclosure) and offered skills for non-disclosure, if desired. Otherwise, she was administered the module on partner communication (A) which offered communication skills such as 'I' statements and other conflict negotiation tactics. All participants were guided to develop action plans at the end of the initial session to apply some of the skills they gained during the session to their lives. Counselors also provided referrals, including "warm referrals" (referrals with escort), as needed, to organizations in the community for additional services (e.g. psycho-social, legal, medical), including warm referrals.

For the booster session at the month 1 HOPE visit, CHARISMA counselors followed up on progress around action plans (i.e., whether participants were able to take action and what happened), checked in on referral uptake (i.e. uptake of and experience with referrals services), and offered booster counseling according to the participants' needs. CHARISMA counselors collected follow-up HEART data at participants' month 3 and month 6 HOPE visits. If participants reported having a new partner at any time during the follow-up period, the HEART and counseling were readministered. If participants reported experiencing IPV at any time during follow-up, they were provided with IPV counseling and referrals, as needed.

Male engagement activities—Women participating in the CHARISMA pilot study were encouraged to invite their partners to come to the clinic for either individual or couples counseling and HIV counseling and testing. [14].

Measures—Data captured from the HOPE visit on Case Report Forms (CRFs) were used to assess how CHARISMA impacted key outcomes of interest. CRFs were interviewer-administered at enrollment and scheduled follow-up visits at Months 3, 6, 9 and the last study visit (month 12 for participants who exited as scheduled). Variables of interest were defined as follows:

- *Disclosure* Participants were asked at each visit whether her primary sex partner knew that she had been offered to use a vaginal ring as part of this study. Answer options were “Yes”, “No”, and “Not sure”.
- *Partner research clinic attendance* was defined by whether a participant reported that her primary sex partner had come to the study clinic in the past month.
- *Social harms (SH)* To assess SH, participants were asked a standardized yes/no question about whether at any time during the past three months, they had experienced a negative change, event, or experience in their life related to their study participation. Women could also spontaneously report SH at any study visit.
- *IPV* was defined by participant response to a standardized question adapted from the WHO Violence Against Women Survey (VAWS) [18] with three parts regarding whether their primary sex partner or any other current or previous partner had ever committed acts of physical or sexual violence against them within the past three months. A woman was classified as having experienced IPV if she responded yes to any of the three question parts.
- *Product adherence* was measured by the amount of residual dapivirine levels in used rings, collected at each clinic visit. Rings contain 25 mg of dapivirine and release approximately 4 mg during a month of continuous use. Used rings were tested for dapivirine with the use of acetone extraction and high-pressure liquid chromatography (Parexel). The amount of dapivirine released was calculated by subtracting the residual levels of dapivirine in each ring from the level documented at the time of manufacturing. [19]. Relative levels of adherence were indicated based on residual dapivirine levels in used rings of ≤ 1.4 mg, 1.4 – 3 mg, 3 – 3.9 mg, and ≥ 3.9 mg, respectively., Post-hoc, non-randomized analyses from ASPIRE suggested that adherence was associated with HIV risk reduction [20].

Analytic Approach

The purpose of our analyses was to evaluate the preliminary impact of the CHARISMA intervention. We summarized data for the above key outcomes at the CHARISMA site. Subsequently, we used a nonrandomized quasi-experimental approach to compare each of the pilot study outcome variables between the Wits RHI intervention site and three comparison sites also participating in HOPE. These sites were selected because they were most similar to the Wits RHI site in terms of ASPIRE and HOPE baseline data pertaining to key indicators including incidence of IPV, proportion of participants who disclosed ring use, male partner clinic attendance, demographics (age, marriage, and cohabitation status), social harms reported, and ring adherence. Thirteen sites were considered in total. The

three comparators were all in South Africa. For each outcome, we present descriptive statistics and bivariable (unadjusted) and multivariable (adjusted) regression models. All regression analyses used Wits RHI as the reference site, and present effect estimates for each of the three comparison sites relative to Wits RHI. The multivariable models adjusted a priori for age and time in study. We also evaluated the following baseline variables as potential confounders for each model based on the literature and our conceptual framework: education, income, partner HIV status, cohabitation with partner, financial support from partner, age difference with partner, any transactional sex in the past year, and reports of IPV in the past year and disclosure of ring use at baseline. Because of the relatively small number of participants and events per site, our modeling approach aimed to fully control for confounding while maintaining parsimony in the number of variables in the final model. For the disclosure, IPV, and adherence models, we started with models that adjusted for all potential confounders and then eliminated variables when doing so did not lead to meaningful changes in the effect estimates from the full model. For the social harms and clinic attendance models, which had very small numbers of events, we chose a smaller subset of potential confounders to include a priori.

Ring Disclosure

We calculated the proportion of visits where a participant reported her partner was aware that she has been offered to use a VR as part of the study (versus not aware or unsure), by study site, stratified by baseline report of partner awareness. The relative awareness of disclosure at each follow-up visit was compared between the intervention site and each comparator site using generalized estimating equations (GEE) Poisson regression with exchangeable correlation matrix and robust standard errors to account for multiple measures per participant. The final multivariable model controlled for disclosure to primary partner at baseline, age, and time in study.

Partner Clinic Attendance

We calculated descriptive statistics for the proportion of women reporting any partner clinic attendance during study follow-up. Risk ratios were calculated using exact Poisson regression models, with separate models for each comparator site compared to the intervention site as reference group. The multivariable model adjusted a priori for age, time in study, and baseline measures of cohabitation with partner and financial support from partner.

Social Harms

The proportion of women experiencing any partner-related SH during the study and partner-related SH incidence rates were calculated using exact Poisson regression model. An offset for time from enrollment to onset of first SH was incorporated, with separate models for each comparator site compared to the intervention site as reference group. The multivariable model controlled a priori for age, baseline partnership status (cohabiting with partner, or not cohabiting with partner), and baseline partner awareness of ring.

IPV

The proportion of women reporting any IPV during study follow-up was calculated by site. Additionally, risk ratios for IPV were calculated using Poisson regression models with robust standard errors. The final multivariable model adjusted for age, time in study, education, income, baseline measures of any IPV, cohabitation with partner, financial support from partner, and transactional sex.

Product Adherence

Ring dispensations and returns were conducted at monthly visits for the first study quarter and batched at subsequent quarterly visits. Therefore, we calculated an average residual ring level for each study visit, using all rings returned at that visit. A total of 3792 rings were dispensed to participants at the 4 selected study sites. We excluded rings that were not tested due to lab error (n = 5, 0.14%) and all rings from study visits where more than the expected number of rings were returned (n = 92; 2.43%). An additional 96 rings (2.54%) were either not returned or returned but not stored; the most common reason that rings were not stored was because they were unused. Therefore, we assumed that non-returned or nonstored rings were unused. To include them in the analysis, we imputed a random value for the amount of dapivirine released from a normal distribution with mean of 0 and SD of 0.1. Overall, our analysis included 3685/3782 rings (96.62%), including 3589 tested rings and the 96 unreturned or untested rings with imputed values, combined into 1955 endpoints representing monthly (study months 1–3) or quarterly (study months 4–12) visits.

Adherence was analyzed as a continuous variable. We calculated descriptive statistics for the amount of dapivirine released from the rings at each study site, including the mean, standard deviation, median, and interquartile range. We used GEE linear regression models with robust standard errors and an exchangeable correlation matrix to compare adherence levels across sites. The final multivariable model adjusted for age and time in study.

To address the risk of uncontrolled confounding, we conducted a sensitivity analysis in which we controlled for adherence levels in the ASPIRE trial, the parent clinical trial from which HOPE participants were enrolled. This analysis excluded the participants from the placebo arm of ASPIRE, for whom residual ring data was not available. For each active arm participant, residual ring levels were averaged over the last 12 months of ASPIRE participation to create a single variable, and this variable was included in a multivariable regression model with adherence levels from the HOPE trial as the outcome. Adjusting for ASPIRE adherence levels did not create any meaningful differences in the point estimates or confidence intervals.

Results

At Wits RHI, 95/96 participants (99%) agreed to participate in the CHARISMA intervention. At enrolment, following completion of the HEART and counselor judgment, 57.9% received counseling from the IPV module, 32.6% received disclosure counseling, and 28.4% received the partner communication counseling. Proportions do not tally to 100% because some individuals, based on time and need, were given counseling from more than

one module. Among the 84 HOPE participants who came for their Month 1 visit, over half (n = 52, 61.9%) were recommended to receive booster counseling: 50% for IPV, 26.9% for disclosure and 34.6% for partner communication). Follow-up counseling was indicated for 51.1% of the 86 who presented for Month 3 (43.2% for IPV, 25.0% for disclosure, 34.1% for partner communication), and 34.8% of the 89 HOPE participants who came for their Month 6 visit (38.7% for IPV, 41.9% for disclosure, 25.8% for partner communication).

The characteristics of the study sample are presented in Table 1. Mean age was 30, 36.8% lived with a partner, and 85.3% received their partner's financial support. Almost one quarter of women in the study had attended college or university (24.0%), and almost half had completed secondary school (45.8%). More than 80% of the participants were unmarried. Women at Wits RHI were different than women at the other three sites in regards to being more likely to be married and living with their partner, more likely to report consuming alcohol, and more often reporting they "didn't know" their primary partner's HIV status. Women at Wits RHI and Site C, both urban locations, had a higher level of education on average, but less likely than their counterparts at Sites A and B to be earning their own income. Across all 4 sites (Wits RHI and 3 comparators), retention was > 95% at each HOPE visit.

The pilot study data will be presented first by the male engagement outcomes of ring disclosure and clinic attendance; followed by safety-oriented outcomes of SH and IPV experiences; and finally by their adherence behavior.

Partner Engagement

Ring Disclosure—A substantial proportion of women (60.4%) at Wits RHI reported at enrollment that their primary partner knew that she was using the ring, and partner awareness of ring use was reported at 72.7% of follow-up visits. At most (92.5%) of the follow-up visits where the partner had been aware of the ring at baseline, women also reported awareness during follow-up. Follow-up disclosure was also reported at 39.4% of visits among women whose partner was not aware of the ring at baseline (Table 2).

By contrast, at comparator sites, 67.2%–84.4% of participants reported during follow-up that their primary partner knew that they had been offered to use a VR as part of this study (Table 2). In regression analyses of disclosure, adjusting for age, time in study, and baseline levels of partner ring awareness, there were no significant differences between the Wits RHI and the comparator sites, although findings for Site B vs. Wits RHI were marginally statistically significant, with women at Site B being 12% more likely to report partner awareness of ring use at follow-up visits compared to women at Wits RHI (aRR 1.12, 95% CI 1.00–1.25, p = 0.053).

Partner Clinic Attendance

At enrollment, there were no women at Wits RHI who reported primary partner clinic attendance in the prior month during the screening window. During follow-up visits, this increased to four women reporting partner attendance in the previous month at least once (4.3%). In each of these four cases, the male partner attended the clinic only once.

Male clinic attendance at comparator sites was also low. At enrollment, site C had 3 male partners visit in the month prior to enrollment. In the follow-up period, the number and proportion of women whose partner attended the clinic during follow-up was 0 (0%) at Site A, 1 (1.3%) at Site B, and 1 (0. 8%) at Site C. The difference between the proportion of women at Site A and Wits RHI reporting partner attendance was marginally significant (p = 0.058) while the other comparisons were not significant. In regression analysis, the probability of partner attendance was much lower at all three comparison sites than at Wits RHI and this difference was marginally statistically significant at Site A (aRR 0.12, 95% CI 0.00–0.98, p =0.046 (Table 3).

Safety-Oriented Outcomes

Social Harms—One partner-related social harm was reported at Wits RHI, which translates to an incidence rate of 1.20 (95% CI: 0.17–8.50).

Table 4 shows the proportion of women experiencing partner-related SH by site, and incidence rates with 95% CIs. The incidence is highest at Site A, at 3.47 SH per 100 person years, and lowest at Site C (0.87 per 100 person-years), but the numbers are small, and the confidence intervals wide. Table 4 shows the incidence rate ratios for SH at each comparator site compared to Wits RHI. The rates at Site A and Site B were higher than at Wits RHI, and the rate at Site C was lower, but none of the differences were significant.

Intimate Partner Violence (IPV)—At Wits RHI, 11 (11.5%) women reported having experienced any lifetime IPV at baseline, and 9 (9.5%) reported IPV during follow-up (Table 5), including four of whom had reported IPV at baseline, and 5 who had not.

At the comparator sites, between 3 (2.3%, Site C) and 12 (15.00%, Site B) IPV cases were reported at baseline, and between 2 and 9 cases during follow-up, following a similar pattern to the baseline reporting. In regression analysis, there were no significant differences in the risk of IPV during follow-up at Site A or Site B versus Wits RHI. The risk of IPV during follow-up was marginally significantly lower at Site B (aRR 0.20, 95% CI 0.04–0.98, p = 0.047; Table 5).

Women's Adherence Behavior

Ring Adherence—For the 744 used rings returned to Wits RHI, the amount of dapivirine released averaged 3.55 μg of dapivirine (standard deviation (SD) 1.66, 95% CI: 3.43–3.67, Table 6). Mean dapivirine released at Wits RHI was greater than the comparator sites, which ranged from 3.08 to 3.28, suggesting higher adherence levels (Table 6). However, there were no meaningful differences in adherence between Wits RHI and the other sites in an unadjusted or adjusted models.

Discussion

The CHARISMA behavioral intervention of tailored relationship counseling aims to complement delivery of biomedical HIV prevention technologies to enable their improved uptake, adherence, and sustained use among African women. In this pilot study, we offered the CHARISMA intervention to all women participating at the Wits RHI, Johannesburg site

of the HOPE dapivirine vaginal ring trial. The intervention had high uptake and was found to be acceptable and feasible to deliver, as reported previously [15]. More than half of the participants received the “responding to IPV” module at baseline, and throughout the study, based on the responses to the HEART assessment tool and counselor recommendation. However, a substantial proportion of women did not require IPV counseling, and many were not identified as needing supplemental counseling following the initial enrolment session. Although not designed or powered to statistically measure effects, the assessment of the preliminary effect of the intervention on measures of male engagement, safety and ring adherence in this pilot offers several important insights.

First, in terms of partner engagement, many women reported having disclosed ring use to their partners at baseline and during follow-up, which meant that he (reportedly) was aware she was using the ring at study visit time points. Provision of the CHARISMA intervention was not associated with an increase in partner’s ring awareness, however the proportion of women who were exposed to the disclosure counseling module – based on not having already disclosed, and not experiencing IPV—was approximately one-third of the sample at baseline. Further, the counseling did not overtly promote disclosure, so the interpretation of these data is not straightforward. CHARISMA’s counseling on ring disclosure focused on helping women decide for themselves whether they wanted to disclose ring use to their male partner, or whether they wanted to use the study product discretely – one of the core tenets of female-controlled microbicides [21–24]. Strategies and skills for disclosing ring use were developed with participants, as were skills for how to use the ring without a partner’s knowledge, if that was desired. Disclosure has been well characterized in the literature as not simply a single-time event, but a process, and one that can reflect complex interpersonal dynamics [25]. One of the most critical components of disclosure, that CHARISMA aimed to emulate and reinforce, is that the decision to disclose reflects women’s agency to use HIV prevention. [22] Future studies should incorporate measurement of a woman’s conscious and empowered decision to *not disclose* so as to offer greater insight into disclosure intentionality.

Few male partners came to the research clinic. Wits RHI was slightly more successful than the comparator sites in having men attend, however there was still only a small proportion (<10%) who presented. Male partners’ clinic attendance has historically been very challenging for clinical trials of female-initiated HIV prevention methods [26]. Some studies have provided invitation letters, study identification cards, and offered visit fast-tracking, single or couples counseling and optional testing for sexually transmitted infections and HIV. Nevertheless, few studies have reported more than 10% of partners ever attending a clinic visit. [6, 24, 26–29] Anecdotally and in qualitative studies, women indicate that their partners cannot attend because of conflicts with their work schedules or that they do not like coming to a female-dominated setting like the research clinic [24, 30]. It is possible that women do not invite their partners for a variety of reasons such as trying to avoid potential conflict; preserving her privacy, including all the details of study participation; or wanting simply not to bother with involving him. In this pilot study of the CHARISMA intervention, women were reminded they could invite their partners to the clinic, and we conducted a series of parallel activities to men in the community [31], but more directed measures to encourage male partner engagement in the study were not taken.

Women's safety was measured through assessments of social harms and IPV. There is some overlap in these measures, as IPV experienced during the study would have been categorized as an SH if it was directly related to study participation. Social harm reporting was generally low across the HOPE sites, with only six partner-related SH recorded. Our previous SH research has concluded that SH in research trials of female-controlled HIV prevention methods has generally been low, suggesting that use of the ring and participation in research itself does not cause substantial risk among those who choose to join [32]. That said, prevalence of recent IPV, regardless of relation to study participation, was high at these South African sites: approximately 10% of participants reported experiencing some type of IPV in the 12 months prior to HOPE, and almost 7% reported experiencing IPV in the 12 months during HOPE. IPV was not measurably lower at Wits RHI relative to the sites without the CHARISMA intervention. However, these data are also somewhat difficult to interpret because CHARISMA counseling sensitized participants to broader definitions of and acts of violence, including, for example, slapping and pulling hair, that may not have previously been considered to be examples of violence. Consequently, women exposed to this information through the CHARISMA intervention, while increasing their skill sets to prevent IPV, were also increasing their knowledge of what could be considered as IPV and thus may have increased their reporting of IPV.

Finally, ring adherence at the Wits RHI site was higher than at other locations, although not statistically significant at the $p<0.05$ level. The HOPE study aimed to encourage and promote consistent ring use throughout the trial [13]. Although CHARISMA was not significantly associated with adherence, the counseling offered skills to overcome partner-related barriers to ring use and was consistent with other strategies to address well-documented impediments to adherence in HIV prevention trials.

These pilot study results are limited by the fact that we were unable to have an experimental design and the sample size was small. Consequently, we developed a strategy to compare our key outcomes to those from sites that most closely represented Wits RHI but that did not have the CHARISMA intervention. It is possible these sites were inappropriate comparators. Additionally, with this design there is an increased risk of residual confounding that could not be controlled by adjusting for the variables collected by the study, especially with small sample size. Another potential limitation is that the amount of dapivirine released is an imperfect measure of adherence. Nevertheless, our interpretation of these adherence data was consistent with the most current methods of interpreting residual dapivirine levels in used rings. The counseling model offered through CHARISMA as a single session plus booster may not have provided adequate time and support to confer the skills needed to make measurable changes. Finally, because we conducted this pilot study within HOPE, participants at all sites already received protocol-driven adherence support counseling, making measurement of an added effect of CHARISMA counseling more difficult than in a non-trial setting.

These preliminary, pilot study results suggest that male partner disclosure was fairly high among women, yet IPV prevalence was also high before and during the trial, and male clinic attendance was low, demonstrating the need for a behavioral intervention to address relationship dynamics and help facilitate adherence to HIV prevention methods, including

the ring and oral pre exposure prophylaxis (PrEP). As reported elsewhere, the CHARISMA intervention was perceived as helpful and relevant to participants and staff at Wits RHI [31]. A randomized-controlled trial to rigorously test the impact of CHARISMA versus control on relationship communication, support, IPV, SH and PrEP adherence is underway.

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Table 1

Baseline characteristics of the study sample

N	Wits RHI 96		Site A 98		Site B 80		Site C 131		Total 405	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Mean age	30.9	7.0	29.4	6.6	30.4	6.7	28.3	5.9	29.6	6.6
Age difference with partner	4.9	3.8	4.0	4.2	4.2	5.3	3.6	3.4	4.1	4.1
	n	%	n	%	n	%	n	%	n	%
Highest level of education										
Primary school	3	3.1	7	7.2	5	6.3	0	0.0	15	3.7
Secondary school, not complete	26	27.1	39	39.8	30	37.5	25	19.1	120	29.6
Secondary school, complete	44	45.8	47	48.0	36	45.0	79	60.3	206	50.9
Attended college or university	23	24.0	5	5.1	9	11.3	27	20.6	64	15.8
Currently married	19	19.8	13	13.3	5	6.3	11	8.4	48	11.9
Had primary partner at baseline	95	99.0	94	95.9	78	97.5	129	98.5	396	97.8
New primary partner since ASPIRE	3	3.2	2	2.1	2	2.6	0	0.0	7	1.8
Lives with primary partner	35	36.5	18	18.4	18	22.5	23	17.6	94	23.2
Participant earns own income	42	43.8	73	74.5	50	62.5	56	42.7	221	54.6
Primary partner provides financial support	81	85.3	77	81.9	71	91.0	112	86.8	341	86.1
Primary partner's HIV status										
HIV positive	4	4.2	2	2.0	2	2.5	6	4.6	14	3.5
HIV negative	53	55.2	56	57.1	59	73.8	87	66.4	255	63.0
Participant does not know	38	39.6	36	36.7	17	21.3	36	27.5	127	31.4
Number of alcohol drinks per week										
0 drinks	59	61.5	87	88.8	61	76.3	107	81.7	314	77.5
1–7 drinks	32	33.3	11	11.2	18	22.7	21	16.1	82	20.3
8 + drinks	5	5.0	0	0.0	1	1.3	3	2.3	9	2.1
Number of sex partners other than primary, past 3 months										
0 sex partners	74	77.1	65	66.3	70	87.5	115	87.8	324	80.0
1 sex partner	20	20.8	30	30.6	9	11.3	14	10.7	73	18.0
2 + sex partners	2	2.0	3	3.1	1	1.3	2	1.5	8	1.9

Table 2

Participants reporting that partner is aware that she has been offered to use a ring as part of the study

	Proportion of visits with partner awareness of ring use stratified by baseline (BL) report of partner awareness												Relative risk of partner awareness of ring use							
	Partner not aware at BL			Partner aware at BL			No partner at BL			Total			Unadjusted				Adjusted**			
Site	N	n	%	N	n	%	N	n	%	N	n	%	RR	95% CI	Z	p	RR	95% CI	Z	p
Wits RHI	127	50	39.37	213	197	92.49	1	1	100	341	248	72.73	ref				ref			
A	145	52	35.86	224	195	87.05	3	3	100	372	250	67.20	0.93	0.78–1.10	−0.85	0.395	0.95	0.83–1.08	−0.79	0.430
B	88	47	53.41	203	198	97.54	4	4	100	295	249	84.41	1.17	1.02–1.35	2.17	0.030	1.12	1.00–1.25	1.93	0.053
C	137	60	43.80	333	326	97.90	4	4	100	474	390	82.28	1.15	1.01–1.31	2.03	0.042	1.09	0.98–1.21	1.63	0.102

Descriptive statistics and relative risk, by study site

N = 1482 visits among 394 participants*

* Exeludes 11 participants had no follow-up assessments or never reported a primary partner during follow-up

** Adjusted for baseline partner awareness, age, and time in study

Table 3

Women reporting partner clinic attendance

	Proportion of women reporting partner clinic attendance							Relative risk of clinic attendance during follow-up							
	Baseline			Follow-up			p	Unadjusted				Adjusted**			
Site	N	N	%	N	n	%		RR	95% CI	Suff†	P	aRR	95% CI	Suff†	P
Wits RHI	95	0	0	93	4	4.30	Ref	Ref	–		–	–	–		–
A	92	0	0	95	0	0	0.058	0.19	0.00–1.48	0	0.120	0.12	0.00–0.98	0	0.046
B	78	0	0	78	1	1.28	0.377	0.30	0.01–3.01	1	0.494	0.31	0.01–2.95	1	0.510
C	129	3	2.33	128	1	0.78	0.164	0.18	0.00–1.84	1	0.208	0.11	0.00–1.17	1	0.074

Descriptive statistics and relative risk, by study site (N = 394 participants*)

*Excludes 11 participants had no follow-up assessments or never reported a primary partner during follow-up

**Adjusted for age, time in study, and baseline measures of cohabitation with partner and financial support from partner. There was no additional change when adjusting for baseline clinic attendance. N = 390

†Sufficient test statistic from exact Poisson regression

Table 4

Women reporting partner-related SH

Site	Proportion and incidence of partner-related SH, by site						Incidence rate ratios for partner-related SH during follow-up							
							Unadjusted				Adjusted***			
	Total (N)	Partner-related SH (n)	%	P-Y at risk^	Incidence rate**	95% CI	IRR	95% CI	Suff.†	p	aIRR	95% CI	Suff†	P
Wits RHI	96	1	1.04	83.52	1.20	0.17–8.50	Ref	–		–	Ref	–		
A	95	3	3.16	86.43	3.47	1.12–10.76	2.90	0.23–152.18	3	0.651	2.02	0.16–105.11	3	0.937
B	79	1	1.27	71.73	1.39	0.20–9.90	1.16	0.01–91.39	1	>0.999	0.60	0.01–49.63	1	>0.999
C	130	1	0.77	114.61	0.87	0.12–6.19	0.73	0.01–57.20	1	>0.999	0.78	0.01–59.62	1	>0.999

Descriptive statistics and incidence rate ratios, by study site (N = 400 participants*)

*All analyses of partner-related SH exclude women who never reported a primary partner in the study (n = 5)

**Per 100 person-years, exeludes 1 additional participant from WRHI with no follow-up visits in study

***Controlling for age, baseline partnership status (cohabiting with partner, or not cohabiting with partner), and baseline partner awareness of ring. N = 395

^Calculated as time to first partner-related SH or time from enrollment to last product use visit, if no partner SH reported. For one participant who reported an SH at screening, we counted the event with 1 day of time at risk

†Sufficient test statistic from exact Poisson regression

Table 5

Women reporting IPV

	Proportion of women reporting IPV*						Relative risk of IPV during follow-up						
	Baseline			Follow-up			Unadjusted				Adjusted			
Site	N	n	%	N	n	%	RR	95% CI		P	aRR	95% CI	Z	P
Wits RHI	96	11	11.46	95	9	9.47	Ref	–		–	Ref	–		–
A	98	10	10.20	98	7	7.14	0.75	0.29–1.95	− 0.58	0.559	0.45	0.14–1.45	− 1.34	0.180
B	80	12	15.00	80	8	10.00	1.06	0.43–2.61	0.12	0.907	0.63	0.26–1.53	− 1.03	0.305
C	131	3	2.29	129	2	1.55	0.16	0.36–0.74	− 2.35	0.019	0.20	0.04–0.98	− 1.99	0.047

Descriptive statistics and relative risk, by study site (N = 405 participants at baseline, 402 during follow-up*)

* Follow-up column excludes 3 participants with no follow-up IPV assessments

** Adjusting for age, time in study, and baseline measures of any IPV, education, income, cohabitation with partner, financial support from partner, and transactional sex. N = 400

Table 6

Ring adherence, defined by dapivirine released from ring

	Dapivirine released from ring				Regression analyses of dapivirine released from the ring							
					Unadjusted*				Adjusted**			
Site	N	Mean	SD	95% CI	β	95% CI	Z	P	aβ	95% CI	Z	P
Wits RHI	744	3.55	1.66	3.43–3.67	–	–		–	–	–		–
A	830	3.28	1.65	3.17–3.39	− 0.04	−0.40–0.31	−0.23	0.815	0.00	− 0.36–0.35	−0.01	0.993
B	714	3.08	1.66	2.96–3.20	− 0.26	− 0.62–0.10	− 1.41	0.157	−0.25	− 0.62–0.11	− 1.36	0.175
C	1301	3.14	1.51	3.06–3.22	− 0.18	− 0.49–0.14	− 1.11	0.267	−0.11	− 0.43–0.20	−0.70	0.485

Descriptive statistics and relati ve risk, by study site, (N = 1955 visits among 374 participants)

*31 participants excluded because they never used the ring during the study

**Adjusting for age, time in study