AIDS and Behavior
https://doi.org/10.1007/s10461-021-03286-w

ORIGINAL PAPER

The Influence of Perceived Dapivirine Vaginal Ring Effectiveness on Social Disclosure and Ring Adherence

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Accepted: 23 April 2021

Abstract

We analyzed data from 1428 users of the dapivirine vaginal ring, who participated in the MTN-020/ASPIRE phase III trial and subsequent open-label extension MTN-025/HOPE trial, to examine relationships between perceived ring protection, social disclosures, and self-reported ring adherence. In HOPE, 77% perceived the ring to be highly effective, and this view was associated with speaking: (a) to a greater number of people about the study, (b) with other participants, (c) to more people who were in favor of the ring, and (d) to more people whose opinions were valued. Reported adherence was not directly associated with perceived protection but was associated with disclosing to someone who was in favor of the ring. These findings suggest the importance of women's internalized ideas about the protective benefits of the DVR in sharing information about the ring and the importance of social support on adherence.

Keywords HIV prevention · Dapivirine vaginal ring · Adherence · Social support

Introduction

Oral pre-exposure prophylaxis (PrEP) is currently the only approved biomedical intervention for prevention of HIV in women at risk of HIV [1]. Recently, the dapivirine vaginal ring was shown to confer moderate HIV risk reduction in phase III trials, with risk reduction estimated in post-hoc, non-randomized analyses to be substantially higher among women with biomarker-based evidence of high ring use [2–4]. As a new monthly topical prevention option, the ring should provide women with much needed choice for preventing HIV infection in the near future [2, 5]. In light of the recently received positive opinion from the European Medicines Agency (EMA), approvals are now being sought for use in Africa. Nevertheless, ring adherence in younger women has been a challenge.[2, 6–8] In studies

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Published online: 03 May 2021

of preferences for a biomedical HIV prevention products, efficacy has emerged as one of the most important product attributes [9, 10]. Misunderstandings about the effectiveness of PrEP, including misconceptions that are spread amongst social networks, and negative social norms around use, have been a barrier to the use of PrEP to prevent HIV. [11–13]

Uptake and adherence to HIV prevention products including oral PrEP and the vaginal ring have been shown to be related to social influences such as social support and stigma. Male partners, peers and family have a substantial impact on women's willingness and ability to use HIV prevention products, including on product adherence, in both prosocial and detrimental manners [8, 14–18]. In studies with men who have sex with men (MSM) and with women, PrEP stigma has been a barrier to PrEP uptake [19], acceptability [20, 21], adherence [22], and persistence [22, 23]. Therefore, it is necessary to understand and consider how social influencers might impact product use as products like the vaginal ring are being introduced. Given the novelty of the vaginal ring technology in Africa, and the knowledge of the role of social influencers on adoption and use of new technologies, we sought to understand how information is spread about the dapivirine ring during an open-label extension phase. This, in turn, can inform the next stages of technology adoption, following approval and real-world ring introduction.

We used quantitative data from users of the ring, that is, women enrolled in the MTN-020/ASPIRE phase III trial and in the open-label extension (OLE) MTN-025/HOPE trial, to assess the spread of information about the ring, and how this relates to self-reported product adherence and perceived protection.

Methods

Study Population

Our study uses quantitative data from women who participated in both the ASPIRE and the HOPE OLE trials of the ring. ASPIRE was a phase III, randomized, placebo-controlled clinical trial (2012–2015) to determine the safety and effectiveness of the ring to prevent HIV among sexually active, HIV-negative women [2]. The study enrolled 2629 women between the ages of 18 and 45 years at 15 sites in Malawi, South Africa, Uganda, and Zimbabwe. Women were randomized to receive either the monthly ring or a placebo vaginal ring and were asked to use the study product monthly for at least 12 months. Women returned for monthly follow-up visits where a new ring was provided, and received pregnancy testing, HIV testing, and a package of HIV/STI prevention services. Upon exiting the study, women were asked if they would like to be contacted about a future study of the ring.

HOPE was an OLE trial (2016–2018) after ASPIRE which had demonstrated effectiveness of the ring [2, 3]. HOPE enrolled former ASPIRE participants to further assess the ring's safety, characterize women's use of the active ring, and assess the relationship between adherence and HIV protection [24]. Participants in HOPE were informed of the ASPIRE results as part of the dissemination activities of ASPIRE and as part of the informed consent into HOPE. The HOPE study enrolled 1456 women at 14 sites in Malawi, South Africa, Uganda, and Zimbabwe. To be eligible, women needed to have been a participant in ASPIRE, be HIV-negative at time of HOPE screening, not be pregnant or breastfeeding and agree to use contraception during the study. Women who enrolled in the study were followed for 12 months and were offered the choice to accept the ring or not, at any time during the study.

Our analysis uses data from both HOPE and ASPIRE to assess how perceived protection of the ring influenced participants who spoke about the trials/use of ring within their social networks and how these social disclosures influenced self-reported product adherence. First, we assessed product disclosure before and after demonstrated effectiveness of the ring by comparing social disclosures in the ASPIRE versus the HOPE trials. Second, we assessed relationships within only the HOPE study between perceived ring protection, features of social disclosures and self-reported product adherence. We hypothesized that women who perceived the ring to confer high protection would have discussions with more people, and that they would be more likely to report being adherent because of their perceptions that the ring is highly effective.

Ascertainment of Measures

Questions about social disclosures (used as both an exposure and outcome) were asked in both HOPE and ASPIRE at the last study visit. These included a set of survey questions about who participants had spoken to about the trial during their participation. Specifically, they were asked the number of people they had spoken to about the trial they were exiting (ASPIRE or HOPE) besides clinic staff and reported the characteristics of up to five of these individuals. Characteristics that were reported for each person included their relationship with the participant, the sex of the person (male/female), if the person was a participant in the same trial (yes/no), how important was the person's view about the ring (very important versus a little or not important) and if the person was in favor or against the participant's use of the ring (in favor versus neutral or against). We examined each of these measures dichotomously when exploring relationships between characteristics of each of the social disclosures (outcome) and self-reported adherence (exposure). When examining the relationship between these

characteristics (exposure) and self-reported adherence (outcome) for each participant, we created continuous measures defined as the proportion of the participants' social disclosures (up to five) that were in favor of the ring, whose views were important and that were participants in the same trial.

Subjective perception of protection was reported at baseline for all participants within the HOPE trial. Participants were asked, "how much protection do you feel that the ring can provide against HIV" with three possible response options including "a little," "some," and "a lot." We combined the responses a "little/some" versus "a lot" in the analysis due to the small numbers in these groups and to have better interpretability of results. We used "a lot" to measure perceived high protection. A recent publication indicated that the degree of HIV-1 risk reduction from the ring exceeds 50% and may be as high a as 75% to 91% with greater adherence [4]. In a sensitivity analysis, we found that using three categories resulted in the same conclusions (data not shown). Demonstrated effectiveness was not measured directly but we descriptively compared social disclosures between the ASPIRE and HOPE trials during which there was a change in demonstrated protection of the ring to indirectly assess this.

The outcome of adherence was measured using a self-reported rating of ring adherence from the last visit of the HOPE trial. Respondents were asked to "please rate your ability, over the past 4 weeks, to keep the vaginal ring inserted as instructed" with six response options ("very poor," "poor," "fair," "good," "very good," and "excellent."). This measure was adapted from Wilson et al. and used in previous trials of oral and vaginal HIV prevention products [25–27]. We dichotomized adherence as "very good/excellent" versus "very poor/poor/fair and good" to increase interpretability of results. In a sensitivity analysis, we examined this measure using all six response options and got similar results (data not shown). We use self-reported adherence based on previous work showing correlations between self-reported and biological measures of adherence and because we used a perceived measure of protection [25]. We theorized that perceived protection would be associated with motivation to adhere which would be better measured by self-assessed adherence. Furthermore, the biological measure can discriminate well between use and non-use at the population level but has not been validated yet to accurately distinguish level of use at an individual level [4].

Other covariates that were included in our analysis were asked at baseline in HOPE and include age, currently married (yes/no), level of education (no schooling, primary, secondary, attended college), times the participant has been pregnant (0,1, > 1), and how often in the past 4 months the participant has worried about having enough food (never, rarely, sometimes, often) as a measure of food scarcity. The women were also asked, during follow-up, about disclosure to a partner about the trial and the ring.

Statistical Analysis

Descriptive characteristics of women who chose to participate in both ASPIRE and HOPE were assessed overall and by study. Percentages and frequencies for categorical variables and medians with the interquartile range (IQR) for continuous variables were reported. We then examined characteristics of each of five possible social disclosures, using all contacts reported as the denominator. This allowed us to examine, among all reported contacts, the proportion who were female, were also a participant, were in each relationship category, had an important view, and were in favor of participant's use of the ring.

Next, we used a set of models to explore relationships between perceived protection, social disclosures, and self-reported adherence (Fig. 1). We hypothesized that these relationships would ultimately affect attitudes, misconceptions and social norms around the ring that are spread amongst social networks. We first estimated crude and adjusted prevalence ratios or count ratios for associations between perceived protection in HOPE at baseline (exposure), and

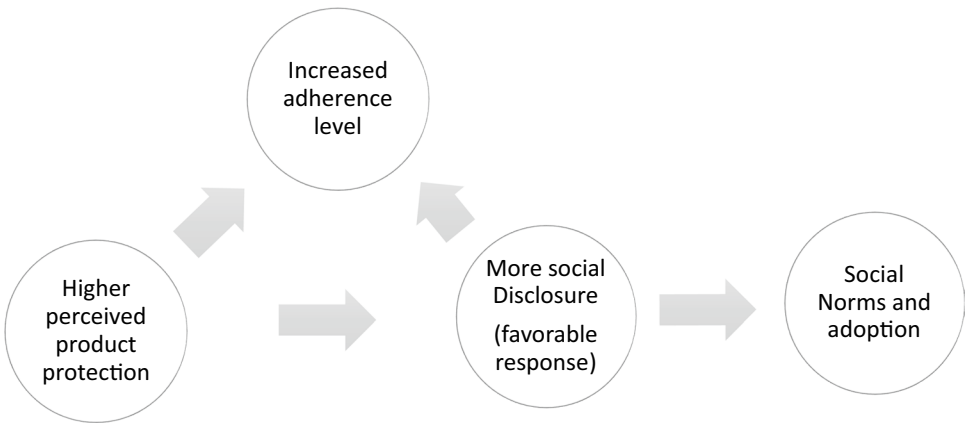

Fig. 1 Conceptual model of relationships between perceived product protection, adherence, and social disclosures

features of social disclosures within HOPE (outcome) that were reported at the final study visit. A Poisson regression model was used to estimate a count ratio for the association between perceived protection and total number of social disclosures as the outcome. We used a log binomial model to estimate prevalence ratios for the association between perceived protection and each disclosure's sex, if they were a HOPE participant, importance of their view about the ring, and if they were in favor of the ring. We used all contacts (participants would report up to five) as the denominator and used generalized estimating equations with an exchangeable correlation matrix to account for multiple social disclosures per person. Adjusted models included age, education level and marital status. We adjusted for these covariates based on an a priori hypothesis that they would be related to disclosure to social networks.

We then examined the proportion of disclosures with a particular characteristic (summarizing over the five possible disclosures) for each individual participant in relation to individual self-reported adherence. We used a log binomial model to estimate crude and adjusted prevalence ratios for the associations between continuous proportions with each characteristic (exposure) and self-reported adherence as a binary variable (outcome). Adjusted models included age, education level and marital status. Lastly, we used a similar approach using log binomial models to estimate crude and adjusted prevalence ratios for the relationship between perceived protection (exposure) and self-reported adherence (outcome).

Results

A total of 1432 women participated in both the ASPIRE and HOPE trials and were included in this analysis of social disclosures, perceived protection, and self-reported adherence. Women were a median of 31 years old (IQR 27, 36), had some secondary education (N = 472; 33%) or completed secondary school (N = 581; 40.6%), and had more than one child (N = 1047; 73.1%) (Table 1). When asked about perceived protection of the ring at enrolment into the HOPE trial, most participants responded that the ring provided a lot of protection against HIV (N = 1095; 76.6%), followed by some (N = 263; 18.4%) and a little (N = 71; 5%).

During ASPIRE, women reported disclosing participation to a median of five people (Inter-quartile range (IQR) 3–10) compared to four in HOPE (IQR 2–5). However, other characteristics of social disclosures were relatively similar between HOPE and ASPIRE (Appendix Table 5). Most disclosures were to people who were female (ASPIRE N = 4458, 78%; HOPE N = 4094, 79%), were not in the trial (ASPIRE N = 4782, 84.0%; HOPE N = 4515, 87.3%) and were a friend (30%), partner (17%) or other family member (28%). Participants spoke with more individuals whose views about the ring were very important (ASPIRE N = 3750, 72.6%; HOPE N = 4257, 74.8%) and most were reportedly in favor of the ring (ASPIRE N = 4835, 85.0%; HOPE N = 4311, 83.6%). Social disclosures who were in favor of the ring in HOPE were more likely to also be a participant (13.9% vs. 5.0%) and had views that was considered important by the participant (81.6% vs. 23.3%) (Appendix Table 6). Compared to ASPIRE, social disclosures in HOPE who were in favor of the ring were less likely to be female (ASPIRE 83% vs. HOPE 80%), be a participant in the study (ASPIRE 18% vs. HOPE 14%), a husband or primary partner (ASPIRE 18% vs. HOPE 15%), and have an opinion viewed by the participant as very important (ASPIRE 85% vs. HOPE 82%), although these differences were not statistically significant.

Table 2 shows the association between perceived protection at entry into the HOPE trial in relation to social disclosures that were reported at the end of the study. Perceived protection was associated with disclosing to individuals who were in favor of the ring (PR 1.04; 95% CI 1.00, 1.08), whose opinion of the ring was important, irrespective if it was a negative or positive opinion, (PR 1.12; 95% CI 1.05, 1.19), and to individuals who were also participants in HOPE (PR 1.56; 95% CI 1.22, 2.00). Perceived protection was not associated with sex of the disclosure. Participants who perceived a lot of protection from the ring at baseline also spoke to a greater number of people about HOPE (Count ratio 0.20; 95% CI 0.15, 0.26), adjusting for age, marital status, and education. Yet, the participant's perceived protection of the ring was not directly associated with their self-reported product adherence (PR 1.08; 95% CI 0.98, 1.20) (Table 3).

Table 4 shows relationships between characteristics of social disclosures and self-reported product adherence. Disclosing to a higher proportion of people who were in favor of the ring was associated with higher self-reported adherence (PR 1.11; 95% CI 1.00, 1.23), after adjusting for covariates. Conversely, we did not find an association between the number of social disclosures, the proportion of social disclosures who were also study participants or the proportion who had a view that was very important, and self-reported product adherence.

Discussion

Characteristics of social disclosures were similar between the HOPE and ASPIRE trials, although participants in ASPIRE disclosed to a higher number of people. In HOPE, perceived protection was associated with having more social disclosures and having social disclosures who were in favor of the ring, had an opinion that the participant viewed as

Table 1 Descriptive characteristics at enrollment visit in HOPE of women who participated in both HOPE and ASPIRE trials (N = 1432)

	Median (IQR)	N (%)
Age	31 (27, 36)	
Currently Married		
Yes		675 (47.1)
No		757 (52.9)
Education level		
No Schooling		15 (1.0)
Primary school, not complete		141 (9.8)
Primary school, complete		102 (7.1)
Secondary school, not complete		472 (33.0)
Secondary school, complete		581 (40.6)
Attended college or university		121 (8.5)
How many times has the participant been pregnant		
0		60 (4.2)
1		324 (22.6)
>1		1048 (73.1)
Worries about having enough food to eat in the last 4 weeks		
Never		1058 (73.9)
Rarely (once or twice)		222 (15.5)
Sometimes (3-10 times)		119 (8.3)
Often (>10 times)		33 (2.3)
Partner knows about HOPE		
Yes		1069 (77.7)
No		306 (22.2)
Not sure		1 (0.1)
Partner knows offered vaginal ring in HOPE		
Yes		941 (68.4)
No		432 (31.4)
Not sure		3 (0.2)
HIV status of partner		
Positive		37 (2.7)
Negative		812 (59.1)
Don't know		527 (38.3)
Chose to participate in HOPE because the ring can protect against HIV		
Yes		1404 (98.3)
No		24 (1.7)
How much protection do you feel that the ring can provide against HIV		
A little		71 (5.0)
Some		263 (18.4)
A lot		1095 (76.6)
Rate your ability, over the past 3 weeks to keep the vaginal ring inserted		
Did not accept		196 (13.70)
Very poor/Poor/Fair		66 (4.61)
Good		242 (16.91)
Very good		216 (15.09)
Excellent		711 (49.69)

*Missing partner knows about study N = 56; partner knows about vaginal ring in study N = 56; HIV status of partner N = 56; chose to participate due to effectiveness N = 4; how much protection can the ring provide N = 2.Adherence N = 1

Table 2 Adjusted and unadjusted prevalence ratios (PR), count ratios and 95% confidence intervals (Cis) for the association between perceived protection of the ring (exposure) and attributes of social disclosures (outcomes) within HOPE

	A little or some protection (N = 1216)	A lot of protection (N = 3944)	Unadjusted	Adjusted**
	N (%)	N (%)	PR (95% CI)	PR (95% CI)
Was the social disclosure in favor of the ring				
Against/ Neutral	21 (28.5)	553 (71.4)	1	1
In favor	967 (22.5)	3332 (77.5)	**1.05 (1.01, 1.09)**	**1.04 (1.00, 1.08)**
How important was the social disclosure's view about the ring				
Very important	802 (66.0)	2935 (74.5)	**1.12 (1.05, 1.20)**	**1.12 (1.05, 1.19)**
Not/ a little important	414 (34.0)	1004 (25.5)	1	1
Social disclosure was also a participant in HOPE				
Yes	106 (8.7)	543 (13.8)	**1.52 (1.20, 1.93)**	**1.56 (1.22, 2.00)**
No	1110 (91.3)	3401 (86.2)	1	1
Sex of social disclosure				
Male	252 (20.8)	818 (20.8)	0.99 (0.90, 1.09)	0.99 (0.89, 1.09)
Female	961 (79.2)	3121 (79.2)	1	1

	Median (IQR)	Median (IQR)	Unadjusted Count Ratio (95% CI)	Adjusted Count Ratio Count Ratio (95% CI)
Number of people spoke to about study besides clinic staff (N = 1432)	4 (2,5)	4 (2,6)	**0.15 (0.09, 0.20)**	**0.20 (0.15, 0.26)** 1

Bold = P < 0.05

**Adjusted for age, education level and marital status; importance of viewpoint missing 5; sex of social disclosure missing 8; in favor of ring missing 8

Table 3 Adjusted and unadjusted prevalence ratios (PR) and 95% confidence intervals (Cis) from the association between perceived protection (exposure) of the ring and adherence (outcome) in HOPE (N = 1432)

	Poor/fair/good adherence	Very good/excellent adherence	Unadjusted	Adjusted**
	N (%)	N (%)	PR (95% CI)	PR (95% CI)
A little or some protection	131 (39.2)	203 (60.8)	1	1
A lot of protection	370 (33.8)	724 (66.2)	1.09 (0.99, 1.20)	1.08 (0.98, 1.20)

**Adjusted for age, education level and marital status

Table 4 Adjusted prevalence ratio (PR) and 95% confidence intervals (Cis) for the association between social disclosures (exposure) and adherence (very good/excellent) (outcome) in HOPE (N = 1432)

	Unadjusted PR (95% CI)	Adjusted** PR (95% CI)
Proportion of social disclosures that are participants	0.92 (0.83, 1.03)	0.93 (0.83, 1.04)
Proportion of social disclosures in favor of the ring	**1.09 (1.00, 1.20)**	**1.11 (1.00, 1.23)**
Proportion of social disclosures' whose view was very important	1.09 (0.99, 1.20)	1.04 (0.97, 1.12)
Number of people spoke to about study besides clinic staff	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)

Bold = P < 0.05

**Adjusted for age, education level and marital status

important, and who were also a participant in HOPE. Those who disclosed to people who were in favor of the ring were more likely to report being more adherent. However, perceiving the ring as highly protective was not directly associated with better self-reported ring adherence.

In July 2020, the ring received a positive opinion by the EMA, in Nov 2020 received prequalification approval from WHO and now is recommended by WHO as part of combination prevention, [28] important steps toward future approvals in low- and middle-income countries. Given that the ring may soon be rolled-out in Sub-Saharan Africa, it is important to consider how subjective perceptions of protection could influence diffusion of information about the ring through social networks and motivate ring adoption. In the OLE HOPE trial women chose to use or not use the ring. Women who perceived the ring to be more effective were more likely to speak with others about the ring, and to speak with people whose opinions they viewed as important. In addition, other studies have shown that positive social attitudes that develop around prevention products within social networks can influence acceptability, and product use [12, 29, 30]. Indeed, a preliminary analysis of HOPE participants suggests that perception of high protection is associated with more uptake of the ring during the trial. [31] Women who think the ring is protective may be more likely to spread information and influence uptake in others. However, it is possible that outside of clinical trials, negative views of the ring may be more relevant to dissuading others from use. This highlights the importance of providing clear and understandable messaging about ring attributes, including level of effectiveness, especially for products that may confer partial protection like the ring. Clear messages should include information about how protection might relate to behaviors like continuous use of the ring. [4] For example, a recent study found that at least some ring use was associated with a 48% (95% CI 21% to 66%) relative reduction in HIV-1 acquisition risk but protection could be as high as 75% to 91% with high adherence [4]. Individual understandings of protection could influence positive social norms and increase product uptake within the greater community.

We found that women in ASPIRE disclosed their study participation to more people than they did in HOPE. Rather than an indication of the demonstrated effectiveness of the ring, women may have disclosed to more people in ASPIRE, before the ring was shown to be effective, because ASPIRE was their first experience using the ring. However, the characteristics of social disclosures did not vary between studies after ring effectiveness was known. Within HOPE, we did not find that perceived protection was associated with reporting of product adherence. This suggests that one's own perceptions of how effective the ring is at preventing HIV may not affect one's own adherence. Alternatively there might be a high level of misclassification in the self-reported measure. [27, 32] However, we did find that better self-reported adherence was related to disclosing to more people who were in favor of the ring. Other studies have shown that women's willingness and ability to use HIV prevention products are highly dependent on social influencers and that product disclosure can have both positive and negative impacts on adherence [15, 16, 18, 33]. Our study adds to these findings by showing that across social disclosures, adherence may be positively influenced by the number of disclosures who are in favor of the ring. Interventions to increase social support after disclosures across social influencers may be important for product adherence.

Further, women who perceived a lot of protection from the ring were more likely to disclose to people who were in favor of the ring. It is possible that perceived protection might have a small, indirect relationship with higher adherence by increasing social support for product use. Perceived protection was also associated with disclosing use to another participant in the HOPE study. A qualitative study of participants in the ASPIRE trial found that women in the study received positive support for ring use from peers in the trial but that external peers reportedly provided negative input that sometimes led to ring removals. [8] It is possible that women in HOPE who perceived a lot of protection from the ring were more motivated to disclose their product use to other trial participants (peers) to seek social support for their own use. Therefore, it is important to ensure correct messaging and understanding because women who have negative perceptions and experiences may discourage uptake, adherence, and persistence among other women.

Our study explores relationships between social disclosures, perceived protection and self-reported product adherence in women who participated in the ASPIRE and HOPE trials. Our analysis relies on data from two clinical trials of the ring to assess social disclosures of information about the ring. Patterns of social disclosures may differ outside of this clinical trial setting because participants in the trial were receiving additional support and information about the ring that will not be available in implementation settings. It is also possible that other social norms will develop once the product is available for wider use in the population and these norms may also influence spread of information and perceived protection of the product. Lastly, we rely on self-reported ratings about product adherence which may differ from biological measures of adherence. Yet, there are limitations of biological adherence measures via drug residual in the ring. We also expect that self-reported adherence might have a stronger relationship with perceptions of protection.

In conclusion, we found that women who perceived a lot of protection from the ring spoke to a greater number of people about the trial, to people whose opinions they valued, who were in favor of the ring, and who were also trial participants. Perceived protection was not directly associated with better self-reported ring adherence signaling that other considerations in addition to efficacy may inform women's level of use [9]. Yet, having more disclosures who were in favor of the ring was associated with better self-reported adherence. These findings highlight the social dimension of

effective HIV prevention and indicate that messaging around product protection could lead women to speak with more people about the ring, potentially influencing acceptability, and uptake in the greater community. Social disclosures that result in a favorable opinion of the ring can influence adherence showing that interventions are needed to reduce stigma and increase positive messaging, across social influencers in whom women are most likely to confide. Experiences of social support may increase adherence and positive perceptions of the product, thereby leading to these users having positive perceptions of the product and effects on future users. Finally, we did not identify a difference in the characteristics of social disclosures before or after ring effectiveness was known. More research is needed to understand how decisions about disclosure and the effects of social influencers vary with real-world ring implementation.

Appendix

See Tables 5 and 6.

Table 5 Characteristics of social disclosures in ASPIRE versus the HOPE trials (N = 7160 possible disclosures reported, up to 5 per person)

	ASPIRE % (N)	HOPE N (%)
What is your relationship with this social disclosure		
Husband or primary partner	988 (17.4)	780 (15.1)
Sex partner other than primary partner	36 (0.6)	82 (1.6)
Mother	479 (8.4)	387 (7.5)
Father	35 (0.6)	33 (0.6)
Other family member	1769 (31.1)	1460 (28.2)
Someone you met during the study	69 (1.2)	72 (1.4)
Neighbor	382 (6.7)	494 (9.5)
Friend	1607 (28.2)	1573 (30.4)
Co-worker	134 (2.4)	192 (3.7)
Other	195 (3.4)	102 (2.0)
Sex of social disclosure		
Female	4458 (78.3)	4094 (79.3)
Male	1233 (21.7)	1071 (20.7)
Social disclosure was a participant in the same study		
No	4782 (84.0)	4515 (87.3)
Yes	902 (15.9)	629 (12.5)
Unknown	6 (0.2)	9 (0.2)
How important was the social disclosure's view about the ring		
Not important	735 (12.9)	703 (13.6)
A little important	696 (12.2)	715 (13.8)
Very important	4257 (74.8)	3750 (72.6)
Was the social disclosure in favor or against the participant using the ring		
In favor	4835 (85.0)	4311 (83.6)
Against	333 (5.85)	401 (7.8)
Neutral	362 (6.36)	373 (7.2)
NA	160 (2.8)	74 (1.4)

Missing- out of the total possible 7160; Relationship to participant in ASPIRE (N = 1466); Relationship to participant in HOPE (N = 1984); Sex in ASPIRE (N = 0); Sex in HOPE (N = 1987); Another participant in ASPIRE (N = 1987); another participant HOPE (N = 1992); importance of view ASPIRE (N = 1472); importance of view HOPE (N = 1472); in favor ASPIRE (N = 2001); in favor HOPE (N = 1470)

Table 6 Characteristics of social disclosures in HOPE (N = 7160 possible disclosures reported, up to 5 per person) by if the disclosure was in favor of the ring

	ASPIRE		HOPE	
	In favor	Against/neutral	In favor	Against/neutral
	% (N)	N (%)	% (N)	N (%)
What is your relationship with this social disclosure				
Husband or primary partner	865 (17.9)	82 (11.8)	638 (14.8)	113 (14.6)
Sex partner other than primary partner	25 (0.5)	4 (0.6)	60 (1.4)	20 (2.6)
Mother	430 (8.9)	42 (6.0)	345 (8.0)	34 (4.4)
Father	29 (0.6)	4 (0.6)	28 (0.7)	4 (0.5)
Other family member	1535 (31.8)	198 (28.5)	1238 (28.7)	209 (27.0)
Someone you met during the study	63 (1.3)	6 (0.9)	57 (1.3)	14 (1.8)
Neighbor	316 (6.5)	48 (6.9)	398 (9.2)	84 (10.9)
Friend	1331 (27.5)	239 (34.4)	1316 (30.5)	236 (30.5)
Co-worker	85 (1.8)	47 (6.8)	144 (3.3)	47 (6.1)
Other	156 (3.2)	25 (3.6)	85 (2.0)	13 (1.7)
Sex of social disclosure				
Female	4006 (82.8)	622 (89.5)	3433 (79.8)	602 (77.9)
Male	829 (17.1)	73 (10.5)	868 (20.2)	171 (22.1)
Social disclosure was a participant in the same study				
No	3947 (81.7)	677 (97.4)	3703 (85.9)	734 (94.8)
Yes	880 (18.2)	17 (2.4)	600 (13.9)	600 (5.0)
Unknown	5 (0.1)	1 (0.1)	6 (0.1)	1 (0.1)
How important was the social disclosure's view about the ring				
Not important	333 (6.9)	303 (43.6)	329 (7.6)	357 (26.1)
A little important	402 (8.3)	268 (38.6)	462 (10.7)	237 (30.6)
Very important	4095(84.8)	124 (17.8)	3520 (81.6)	180 (23.3)

Missing- out of the total possible 7160; Relationship to participant in ASPIRE (N = 1466); Relationship to participant in HOPE (N = 1984); Sex in ASPIRE (N = 0); Sex in HOPE (N = 1987); Another participant in ASPIRE (N = 1987); another participant HOPE (N = 1992); importance of view ASPIRE (N = 1472); importance of view HOPE (N = 1472); in favor ASPIRE (N = 2001); in favor HOPE (N = 1470)

Acknowledgements ASPIRE/MTN-020 and HOPE/MTN-025 Study Team Leadership: Jared Baeten, University of Washington (Protocol Chair); Thesla Palanee-Phillips, Wits Reproductive Health and HIV Institute (Protocol Co-chair); Nyaradzo Mgodi, University of Zimbabwe College of Health Sciences Clinical Trials Unit (Protocol Co-chair); Elizabeth Brown, Fred Hutchinson Cancer Research Center (Protocol Statistician); Lydia Soto-Torres, US National Institute of Allergy and Infectious Diseases (Medical Officer); Katie Schwartz, FHI 360 (Clinical Research Manager), Ashley Mayo, FHI 360 (Clinical Research Manager).

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Data management was provided by The Statistical Center for HIV/AIDS Research & Prevention (Fred Hutchinson Cancer Research Center, Seattle, WA) and site laboratory oversight was provided by the Microbicide Trials Network Laboratory Center (Pittsburgh, PA). The vaginal rings used in this study were developed and supplied by the International Partnership for Microbicides (IPM).

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Author Contributions MCDS, AvdS contributed to the conception, design of the analysis and writing of the paper. E.B. provided statistical support on the analysis. The remaining authors were involved in data acquisition, data collection, study management and design of the original parent study. All authors have reviewed the paper, provided comments and edits to the manuscript and have read and approved the final manuscript.

Funding The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank the study participants as well as the ASPIRE/HOPE Study team members who implemented the trials.

Data Availability Data are available through the Microbicide Prevention Trials Network.

Code Availability Code for this project is available by contacting the corresponding author.

Declarations

Conflict of interest We declare no competing interests.

Consent to Participate All participants provided written informed consent.

Ethical Approval The trial protocol was approved by the ethics review committee at each site.

References

1. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410.
2. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med. 2016;375:2121–32.
3. Nel A, Van Niekerk N, Kapiga S, Bekker LG, Gama C, Gill K, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. N Engl J Med. 2016;375(22):2133–43.
4. Browne E, Hendrix CW, van der Straten A, Kiweewa FM, Mgodi NM, Palanee-Phillips T, et al. Greater dapivirine release from the dapivirine vaginal ring is correlated with lower risk of HIV-1 acquisition. JIAS. 2020;23:e25634.
5. Baeten JM, Haberer JE, Liu AY, Sista N. Preexposure prophylaxis for HIV prevention: where have we been and where are we going? J Acquir Immune Defic Syndr. 2013. https://doi.org/10.1097/QAI.0b013e3182986f69.
6. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African Women. N Engl J Med. 2015;372:509–18. https://doi.org/10.1056/NEJMoa1402269 (**[Internet]**).
7. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367:411–22. Available from http://www.ncbi.nlm.nih.gov/pubmed/22784040
8. Katz AWK, Naidoo K, Reddy K, Chitukuta M, Nabukeera J, Siva S, et al. The power of the shared experience: MTN-020/ASPIRE trial participants' descriptions of peer influence on acceptability of and adherence to the dapivirine vaginal ring for HIV prevention. AIDS Behav. 2020. https://doi.org/10.1007/s10461-020-02799-0.
9. Browne EN, Montgomery ET, Mansfield C, Boeri M, Mange B, Beksinska M, et al. Efficacy is not everything: eliciting women's preferences for a vaginal HIV prevention product using a discrete-choice experiment. AIDS Behav. 2020;24(5):1443–51. https://doi.org/10.1007/s10461-019-02715-1.
10. Minnis AM, Browne EN, Boeri M, Agot K, Van Der Straten A, Ahmed K, et al. Young women's stated preferences for biomedical HIV prevention: results of a discrete choice experiment in Kenya and South Africa. J Acquir Immune Defic Syndr. 2019;80(4):394–403. https://doi.org/10.1097/QAI.0000000000001945.
11. Golub SA, Gamarel KE, Rendina HJ, Surace A, Lelutiu-Weinberger CL. From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. AIDS Patient Care STDS. 2013;27(4):248–54. https://doi.org/10.1089/apc.2012.0419.
12. Young I, Flowers P, McDaid LM. Barriers to uptake and use of pre-exposure prophylaxis (PrEP) among communities most affected by HIV in the UK: findings from a qualitative study in Scotland. BMJ Open. 2014;4(11):e005717. https://doi.org/10.1136/bmjopen-2014-005717.
13. Koechlin FM, Fonner VA, Dalglish SL, O'Reilly KR, Baggaley R, Grant RM, et al. Values and preferences on the use of oral pre-exposure prophylaxis (PrEP) for HIV prevention among multiple populations: a systematic review of the literature. AIDS Behav. 2017;21(5):1325–35. https://doi.org/10.1007/s10461-016-1627-z.
14. Palanee-Phillips T, Roberts ST, Reddy K, Govender V, Naidoo L, Siva S, et al. Impact of partner-related social harms on women's adherence to the dapivirine vaginal ring during a phase III trial. J Acquir Immune Defic Syndr. 2018;79(5):580–9. https://doi.org/10.1097/QAI.0000000000001866.
15. Roberts ST, Nair G, Baeten JM, Palanee-Philips T, Schwartz K, Reddy K, et al. Impact of male partner involvement on women's adherence to the dapivirine vaginal ring during a phase III HIV prevention trial. AIDS Behav. 2020;24(5):1432–42. https://doi.org/10.1007/s10461-019-02707-1.
16. Montgomery ET, Van Der Straten A, Chitukuta M, Reddy K, Woeber K, Atujuna M, et al. Acceptability and use of a dapivirine vaginal ring in a phase III trial. AIDS. 2017;31(8):1159–67. https://doi.org/10.1097/QAD.0000000000001452.
17. van der Straten A, Ryan JH, Reddy K, Etima J, Taulo F, Mutero P, et al. Influences on willingness to use vaginal or oral HIV PrEP during pregnancy and breastfeeding in Africa: the multisite MAMMA study. J Int AIDS Soc. 2020;23(6):e25536. https://doi.org/10.1002/jia2.25536.
18. Wagner LD, Roberts ST, O'Rourke S, Celum C, Baeten JM, Bukusi E, et al. Challenges with oral pre-exposure prophylaxis (PrEP) disclosure among adolescent girls and young women (AGYW) in Kenya and South Africa. JAIDS Res Hum Retroviruses. 2018;34:373.
19. Golub SA, Fikslin RA, Goldberg MH, Peña SM, Radix A. Predictors of PrEP uptake among patients with equivalent access. AIDS Behav. 2019;23(7):1917–24. https://doi.org/10.1007/s10461-018-2376-y.
20. Peng P, Su S, Fairley CK, Chu M, Jiang S, Zhuang X, et al. A global estimate of the acceptability of pre-exposure prophylaxis for HIV among men who have sex with men: a systematic review and meta-analysis. AIDS Behav. 2018;22(4):1063–74. https://doi.org/10.1007/s10461-017-1675-z.
21. Calabrese SK, Dovidio JF, Tekeste M, Taggart T, Galvao RW, Safon CB, et al. HIV pre-exposure prophylaxis stigma as a multidimensional barrier to uptake among women who attend planned parenthood. J Acquir Immune Defic Syndr. 2018;79(1):46–53. https://doi.org/10.1097/QAI.0000000000001762.
22. Tangmunkongvorakul A, Chariyalertsak S, Rivet Amico K, Saokhieo P, Wannalak V, Sangangamsakun T, et al. Facilitators and barriers to medication adherence in an HIV prevention study among men who have sex with men in the iPrEx study in Chiang

Mai, Thailand. AIDS Care. 2013;25(8):961–7. https://doi.org/10.1080/09540121.2012.748871.
23. Liu A, Cohen S, Follansbee S, Cohan D, Weber S, Sachdev D, et al. Early experiences implementing pre-exposure prophylaxis (PrEP) for HIV prevention in San Francisco. PLoS Med. 2014;11(3):e1001613. https://doi.org/10.1371/journal.pmed.1001613.
24. Baeten J, Palanee-Phillips T, Mgodi N, Mayo A, Nel A, Rosenberg Z, et al. High uptake and reduced HIV-1 incidence in an open-label trial of the dapivirine ring. In: Confrence on Retroviruses and Opportunistic Infections (CROI); 2018 Mar 4–7; Boston, Massachusetts.
25. Mensch BS, Richardson BA, Husnik M, Brown ER, Kiweewa FM, Mayo AJ, et al. Vaginal ring use in a phase 3 microbicide trial: a comparison of objective measures and self-reports of non-adherence in ASPIRE. AIDS Behav. 2019;23(2):504–12. https://doi.org/10.1007/s10461-018-2261-8.
26. Wilson IB, Lee Y, Michaud J, Fowler FJ, Rogers WH. Validation of a new three-item self-report measure for medication adherence. AIDS Behav. 2016;20(11):2700–8. https://doi.org/10.1007/s10461-016-1406-x.
27. Mensch BS, Brown ER, Liu K, Marrazzo J, Chirenje ZM, Gomez K, et al. Reporting of adherence in the VOICE trial: did disclosure of product nonuse increase at the termination visit? AIDS Behav. 2016;20(11):2654–61. https://doi.org/10.1007/s10461-016-1312-2.
28. International Partnership forMicrobicides. IPM's dapivirine ring for women's HIV prevention receives WHO prequalification. 2020 [cited 2020 Dec 8]. Available from https://www.ipmglobal.org/content/ipm's-dapivirine-ring-women's-hiv-prevention-receives-who-prequalification
29. Cairns GP, Race K, Goicochea P. PrEP: controversy, agency and ownership. J Int AIDS Soc. 2016. https://doi.org/10.7448/IAS.19.7.21120.
30. Koechlin FM, Fonner VA, Dalglish SL, O'Reilly KR, Baggaley R, Grant RM, et al. Values and preferences on the use of oral pre-exposure prophylaxis (PrEP) for HIV prevention among multiple populations: a systematic review of the literature. AIDS Behav. 2017;21:1325–35. Available from https://www.scopus.com/inward/record.uri?eid=2-s2.0-85000785127&doi=10.1007%2Fs10461-016-1627-z&partnerID=40&md5=cc47a59dd09f09e723e4cc32da4467ca
31. Gati Mirembe B, Cabrera MV, Cobbing M, Mgodi N, Palanee TP, Mayo A, Dadabhai S, Mansoor LE, Siva S, Nair G, Akello CA, Nakabiito C, Soto-Torres LE, van der Straten A, Baeten JM, et al. Correlates of dapivirine vaginal ring uptake and acceptance among women participating in an open label extension trial-MTN-025/HOPE. In: 4th HIV Res Prev Conf (HIVR4P). Virtual; 2020. https://programme.hivr4p.org/Abstract/Abstract/605.
32. Van Der Straten A, Brown ER, Marrazzo JM, Chirenje MZ, Liu K, Gomez K, et al. Divergent adherence estimates with pharmacokinetic and behavioural measures in the MTN-003 (VOICE) study. J Int AIDS Soc. 2016;19:20642.
33. Velloza J. The influence of HIV-related stigma on PrEP disclosure and adherence over time among AGYW in HPTN 082. Miami, Florida: IAPAC Adherence Conf; 2019.