

OPTIONS CONSORTIUM: Optimizing Prevention Technology Introduction On Schedule

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A Review of Social and Behavioral Factors Influencing
Dapivirine Ring Use

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OPTIONS
OPTIMIZING PREVENTION TECHNOLOGY INTRODUCTION ON SCHEDULE

A Review of Social and Behavioral Factors Influencing Dapivirine Ring Use

Completed, Ongoing, and Planned Studies

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Summary

The purpose of this literature review is to provide a comprehensive overview of social and behavioral findings from dapivirine ring trials and studies to date, to inform an investment case for the dapivirine ring and guide further study to prepare for uptake. The review pays particular attention to completed work on ring acceptability and adherence as that has been the focus of the majority of studies to date, while additionally looking at factors such as partner buy-in, product preferences, and ring delivery. This paper identifies trends and gaps that emerged during the review process, but does not assess the quality of work of each study.

Methodology and Summary of Studies

AVAC collected a total of 49 studies and reviews focused on social and behavioral elements of the dapivirine ring. We searched conference abstracts, peer reviewed journals, partner projects, the IPM/MTN databases, and the AVAC database to gain a comprehensive body of work. The completed studies were conducted between 2010 - 2016, with the vast majority having been published in 2015 and 2016. While this summary focuses on the dapivirine ring specifically, the literature review index includes a few studies on other ARV-based or intravaginal rings as some social and behavioral findings from these studies may be relevant.

The studies reviewed a range of social and behavioral topics, but the majority investigated acceptability and adherence to the ring (36 studies) with an additional 9 studies investigating sexual partner related issues. In OPTIONS-focused countries, 29 studies took place in South Africa, 16 Zimbabwe, and 1 Kenya.

The majority of the studies were conducted using participants from two Phase III safety and efficacy trials: The Ring Study and ASPIRE. Because of this, there is not a great diversity of findings, studies, or conclusions. These two trials illuminated numerous questions pertaining to social/behavioral issues surrounding the ring, but did not provide many answers. Moving forward, results from the follow on open label studies, should be followed closely as they will provide deeper insights into many of the questions raised by the Ring Study and ASPIRE, as discussed in this review.

Specific questions to Inform Investment Case for the Ring

Is there evidence that the Ring might have higher uptake and/or adherence than oral PrEP?

There has not been extensive work explicitly comparing uptake and adherence for the dapivirine ring versus oral PrEP. However, women have repeatedly indicated that longer acting prevention methods are preferable to shorter acting options. In a study conducted

among women from the VOICE-D trial, 81% of women indicated that they preferred a longer acting prevention option such as an injectable, implant, or ring, to an oral tablet or gel. The most important product characteristics were ease of use of product, time needed to complete activity, administered at a clinic versus self-administration, and degree of familiarity with product (Lueke, 2016).

A LSHTM study used a discrete choice experiment (DCE) to measure PrEP preferences for oral, topical (IVR or gel), or injectable among adults, adolescent girls and young women, and FSW. It also investigated the relative importance of HIV protection, STI protection, and pregnancy protection in a product. The results highlight that preferences are substantially different between populations, notably that adolescent girls, “demonstrated a dislike of the vaginal ring,” and most preferred an injectable. FSW valued HIV protection twice as much as adolescent girls and adult women. While the full study has yet to be published, this work illuminates that it may be difficult to generate ring uptake among adolescent girls, and that multi-purpose technologies would be much better received than single purpose (Quaife, 2016).

Similar results were found in a qualitative study conducted among ASPIRE participants, which found, “Diverse PrEP formulations elicited interest in this subsample, with long-acting methods being favored. Despite high interest in the vaginal ring, other vaginal products did not generate much interest. Familiarity, reliability, absence of side effects and low burden in terms of administration and use were determined as important attributes to consider for new PrEP formulations” (van der Straten, 2016).

MTN 034/IPM 045, a planned study, will investigate the prevention needs and preferences of adolescent girls and young women with a focus on the dapivirine ring and oral PrEP. Results from that study will presumably answer, or bring us closer to answering, this question.

Is there evidence that the ring might have other benefits relative to oral PrEP for the user (e.g., side effects, sexual pleasure)?

Again, no studies have explicitly compared oral PrEP and the ring, however a number of recent study results indicate that women are extremely comfortable, and even enjoy using the dapivirine ring. One study investigated the influence of the ring on sexual experiences of women and found that, “The ring had minimal impact on sex for women and their partners with positive experiences reported by some.” (Laborde, 2016). Women reported enhanced libido or sexual pleasure for both them and their partners while using the ring during sex due to a tighter, drier, or wetter vaginal environment. Before use, women and their partners often worried that the ring would negatively affect their sexual experience; however, the majority reported that this view changed after ring use (Malherbe, 2016). This review looked at 4 studies that investigated the effects of ring use on sex, and all concluded similar results.

As mentioned above, MTN 034/IPM 045 will hopefully shed light on this question.

Is there evidence around marketing & communications / demand generation and distribution strategies for the ring? Is it harder to market / deliver the ring than a pill or an injection for which existing systems are already in place?

While no studies directly addressed marketing & communications / demand generation and distribution for the Ring when compared to oral PrEP or an injectable, a number of other results emerged that may provide insights. Results consistently emerged that women (and their partners) had a negative, or incorrect, perception of the ring before using the product – while generally found the ring to be acceptable and non-invasive after use. This implies that, as with many sexual and reproductive health products at initial use, there may be issues with women (and men) generally misunderstanding how the ring will feel and affect them; therefore, messaging around the product will need to be strong and effective to ensure that uptake is strong. One study on ASPIRE participants found community education tools were effective means of facilitating participants' understanding of things such as HIV prevention, family planning, reproductive health and research. As the ring is rolled out, it will be crucial to message the product to mitigate myths and dispel misunderstandings around the product (Ndawula, 2014).

What is known about partner acceptability and related social harm?

This review includes 9 studies that either focus on or mention partner acceptability of the ring. While there are still gaps in this research, the studies demonstrated that with increased partner buy-in and acceptability, women will be much more likely to adhere to the ring (and therefore, less likely to acquire HIV). One study found, “The actual or perceived dynamics of participants' male partner relationship(s) were the most consistently described influence (which ranged from positive, negative and neutral) on participants' acceptability and use of the ring” (Montgomery, 2016). Research shows partner acceptability to be more important in areas where men continue to dominate decisions on sexual health (Kusemererwa, 2016). The more men understand and accept use of the dapivirine ring, the more successful the ring will be.

Conversely, without partner buy-in, ring use can have negative effects on women. Other microbicide studies have indicated that microbicide use has increased women's exposure to social harms such as intimate partner violence. Results from the CHARISMA study in Johannesburg indicated that, “ring use did not present a major source of disagreement for many, however, both men and women highlighted mistrust aligned with ring use” (Hartman, 2016). It will be important to further understand social harms associated with ring use; results from the open label studies of ASPIRE and the Ring Study will further elucidate these questions.

What is known about ease of delivery of the ring? Are there any benefits in regards to health care workers?

This review reveals a gap in research available to answer these questions. A number of studies described the ring as, “a low maintenance HIV prevention method,” (Malherbe 2016) which could theoretically decrease the amount of time health care workers need to spend with users. More robust research is needed to unpack this topic.

Findings

Overcoming “Ring Worry” for rollout

Summary: Researching and analyzing ring worry (general concerns regarding use of the ring) will be crucial to effectively driving uptake and adherence to the ring. One study conducted among ASPIRE participants investigated whether ring worry at baseline was associated with: willingness to use the ring in the future, age, changed ring worry at follow up, and reported non-use of the ring. The study found that general ring worry significantly decreased between baseline and a 3-month follow up; a positive sign for the product. It additionally found that women 18-21 had both more overall ring worry and more specific concerns (sex and social approval, hygiene, etc.) than older women. Moving forward it will be important to first understand deeply the ring worry of young women, and then understand how to message and promote the ring in such a way that diminishes ring worry among potential users. The study concludes, “Assessing if RW (ring worry) correlate with biomarkers of low adherence may inform whether tailored counseling among young women can improve comfort with and use of the ring” (Levin, 2016). Essentially, more research is needed here, but demand generation campaigns for ring will need to be segmented in such a way that the messaging speaks effectively to ring worry pertaining to specific sub-populations of women.

Another study conducted on ASPIRE participants found similar results, “Initial concerns with the physical attributes of the ring and perceived side effects could be proactively addressed in future activities” (Montgomery, 2016). Similar findings emerged from The Ring Study, with one paper stating, “Women initially had concerns with ring use, which diminished over time. These concerns were commonly related to male partner’s reaction to ring use, rather than physical attributes of the ring” (Malherbe, 2016).

Implications: Strong marketing & communications / demand generation campaign will need to accompany rollout of the ring, as misperceptions and concerns with the ring are high among women in general, but particularly high and acute among young women – an obvious target population.

Partner Buy-In and Understanding of Product is Crucial

Summary: As briefly mentioned above, more research is necessary to understand both the extent to which partners need to be “bought-in” to ring use, and effective methods to build buy-in. One of the loudest concerns amongst women before using the ring was that their partner would find out and be upset. One study conducted during The Ring Study investigated community and partner involvement to enhance ring adherence, and found that, “Community awareness and male involvement are important to support women who are participating in a trial and encourage them to adhere to ring use, but community engagement efforts begin with the participants” (Louw, 2014). While this research was specifically conducted among trial participants in a trial setting, it is logical to assume partner and community buy-in will carry heavy importance when the product is rolled out for use among the general public. Individual and group counseling sessions were held with partners to clarify questions of safety and purpose of the dapivirine ring, and more generally around HIV. Wits RHI recognized the importance of male buy-in while conducting the ASPIRE trial, and held couples counseling, male health education workshops, and disclosure sessions. Their study concluded that male partner involvement resulted in, “increase inter-partner communication and sexual health awareness with potential to impact on study retention, product adherence and ultimately study outcomes” (Reddy, 2014). That partner buy-in with the ring is so important, is interesting, as the product is meant to broaden the prevention options available to women. So if the goal is to create a product that allows women complete control of their own destiny, the ring may not be the answer.

Implications: The link between partner/community buy-in and uptake/adherence may be an issue for the ring, and requires thoughtful planning for rollout. This further emphasizes the importance of strong communications/demand generation strategies to increase understanding and acceptability of the product before use.

Need for further, and more diverse, research

Summary: As briefly mentioned above, most of the information available around social and behavioral issues associated with the ring have emerged from ASPIRE and The Ring Study. The follow on open label studies for both trials will delve deeper into some of the trends detailed below. Currently, we know enough to identify trends and deduce hypotheses and conclusions, but deeper investigation is needed to gain useful insights that will inform a successful rollout of the product once it is approved for widespread use.

Implications: OPTIONS will monitor closely the open label studies currently underway, as well as any other social/behavioral ring studies taking place.

Sexual Experience is important and could increase uptake

Summary: The potential for a negative effect on sex was one of the most frequently cited concerns among potential ring users. As stated previously, after using the product women reported it had minimal impact on sex, with positive experiences reported by some women and their partners. Those who did note a difference reported changing sexual positions or

practices, or removing the ring altogether. Women who reported a positive impact cited increased pleasure due to either a tighter, drier, or wetter vaginal environment (Laborde, 2016).

One study was conducted on female condom functionality in the presence of the ring, and found that simultaneous use was safe and did not negatively impact the clinical failure rate of the female condom (Nel, 2016). Another study evaluated male condom functionality in the presence of the ring and found that the products were safe and well tolerated when used concurrently (Leuvenink, 2014).

Implications: It may be inappropriate and ineffective to message the dapivirine ring as a product that could “increase sexual pleasure” but it will be very important to dispel myths that the ring will negatively impact the sexual experience of women and their partners.

Comfortable and Acceptable

Summary: While there is still a lot research to be conducted on acceptability/comfortability of the ring, results so far have indicated that women find the ring to be a desirable prevention method. Many women reported that they “forgot they were using it” (ASPIRE, 2016). An additional study with ASPIRE participants found that, “Despite initial fears about the ring’s diameter and thickness and potential side effects, participants found the ring easy to use and used it consistently. Fears were overcome with ongoing group discussion, counseling and gradual familiarity with ring use through trial progression” (Montgomery, 2016).

Implications: Positive reactions to the ring bode well for rollout of the ring as an acceptable prevention option for women. However, there is still significant concern that even if women report acceptability after using the product for a few months, generating uptake in the first place may be very difficult due to pre-use perceptions. Health professionals will also have a role to play. When women are not part of a clinical trial, will they actively seek out and use the ring? Further time and research should address this concern.

Age and Adherence

Summary: Studies consistently found that ring preferences, beliefs, levels of adherence, and concerns vary depending on the age of the woman using the ring.

Implications: When planning for rollout, implementers must have a comprehensive understanding of the needs of women in each age segment, and strategize rollout accordingly.

Gaps and areas for continued study; current ongoing and planned studies

- *Comparison to oral PrEP* – Based on the studies reviewed in this paper, there is not much evidence that the certain social / behavioral factors will be more positive or negative with the ring than with oral PrEP.
- *Product preferences* – Will women use the ring? What do women value most between HIV, pregnancy, STIs, etc? These questions merit further attention. The LSHTM DCE experiment investigated some of these questions (full study results to be published in 2017), and found, “stimulating demand for new HIV prevention products may require a more a nuanced approach than simply developing highly effective products. A one- size-fits-all package is unlikely to be an effective or efficient means of delivering new products across different populations. These results strengthen evidence calling for the development of multi-purpose technologies” (Quaife, 2016). These results, and others investigating similar questions, should feed into any investment case made for the ring.
- *Effective messaging for the ring* – Uptake may be slow if the misconceptions surrounding ring use continue as they currently stand. Many users are hesitant to use the product due to worries that ultimately prove to be incorrect. Applying learnings from the rollout of the female condom may be appropriate here, and could help prevent some of the possible rollout failures when the product is approved for widespread use.
- *Healthcare worker involvement* – Some have hypothesized that healthcare workers will need to spend less time with patients who use the ring versus other prevention options. Not enough research exists to determine if this is true.
- *Ongoing and planned studies* – There are two studies, MTN 025 and MTN 032, currently being conducted on to further understand adherence, acceptability, and real world questions raised during the ASPIRE and Ring Study trials. Additionally, there is a planned study, MTN 031/IPM 043, that will, “determine if financial incentive conditional on the prior month’s product use promotes adherence to the dapivirine ring”. Another planned study, MTN 034/IPM 045, will investigate the prevention needs and preferences of adolescent girls and young women, with a focus on oral PrEP and the dapivirine ring.

Study Parameters

Broad Social / Behavioral Parameters	
<i>Measures/includes</i>	<i>Total</i>
Acceptability & Adherence	36
Partner Involvement	9
Marketing & Communications	1
Distribution & Delivery	2
Product Preference	6
Contraceptive Interaction	5
Enrollment Metrics	1

Adherence and Acceptability Studies	
<i>Measures / Includes</i>	<i>Total</i>
Comparison of Age Groups	3
Ring Removal	5
Sexual Experience	4
Vaginal Practice	1
Social Harms	1
Ring Worry	6
Methodology for Measuring Adherence	2
Economic Factors	2
Adherence and Effectiveness	2
Device Insertion	1

Partner Involvement	
<i>Measures / Includes</i>	<i>Total</i>
Partner Acceptability	7
Disclosure of Use	2
Partner Buy-In	1

Geographic Setting	
Region	Number of Studies
Sub-Saharan Africa (OPTIONS Countries)	35
<i>South Africa</i>	29
<i>Zimbabwe</i>	16
<i>Kenya</i>	1
Europe	0
North America	9
Asia	0

Type of Ring	
Ring Type	Number of Studies
Dapivirine	40
Other	9

Conclusion

With the conclusion of the Ring Study and ASPIRE, there has been a host of research released on social and behavioral implications for dapivirine ring use. This “first cut” at understanding the preferences and needs of users, their partners, and communities has illuminated trends and questions to be investigated further, but is not enough to comprehensively inform rollout of the product when approved for widespread use.

OPTIONS Consortium

Continued close monitoring of the follow on open label studies for ASPIRE and the Ring Study, as well as others mentioned, will help shape an actionable and accurate investment case for the dapivirine ring.