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A Mixed-Methods Study Examining Adherence to and Acceptability of Intravaginal Rings for HIV Prevention: Behavioral Results of MTN-027

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Abstract

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Intravaginal rings (IVR) containing antiretroviral (ARV) drugs are a promising method for HIV prevention. We triangulated quantitative and qualitative assessments to evaluate the acceptability of four IVRs used continuously for 28 days as part of a Phase I trial (N=48 HIV-negative women; ages 18-45). Adherence was high throughout the trial, yet 30% of participants reported involuntary IVR expulsions followed by re-insertion. Most participants (93.6%) felt comfortable with the IVR being inside their body. Participants reported liking the IVR more (36.2%) or the same amount (55.3%) since starting the study. When given the option of choosing between the IVR and/or a male condom for HIV-prevention, most reported preferring the IVR (n=29, 63.0%), and over a quarter of the sample reported liking them equally (n=12, 26.1%). We observed no differences in IVR acceptability across the study arms. High adherence and acceptability underscores the promise of an IVR as a female-controlled, sustained mechanism for HIV prevention.

Resumen

Un anillo intra-vaginal (AIV) que contiene medicamentos antirretrovirales (ARV) constituye un metodo prometedor para prevenir el VIH. Triangulamos los datos cuantitativos y cualitativos para evaluar la aceptabilidad de cuatro AIV usados continuamente por 28 días durante un estudio clinico Fase 1 (N=48 mujeres seronegativas; entre las edades de 18-45 años). La adherencia fue alta durante el estudio, aunque un 30% de las participantes reportaron expulsiones involuntarias del AIV seguidas por la re-inserción. La mayoría de las participantes (93.6%) se sintieron cómodas con tener el AIV dentro de su cuerpo. La mayoría de las mujeres reportaron que les gustó el AIV más (36.2%) o igual (55.3%) desde iniciar el estudio. Dada la opción de elegir entre el AIV y/o un condón masculino para la prevención del VIH, la mayoría reportó preferir el AIV (n=29, 63.0%), y más de un cuarto de la muestra reportó que ambos métodos les gustaron de igual manera (n=12, 26.1%). No observamos diferencias en la aceptabilidad entre los cuatro anillos. La alta adherencia y aceptabilidad demuestran la promesa que conlleva un AIV como método de prevención del VIH que es controlado por las mujeres y de uso continuo.

Keywords

microbicide; HIV prevention; women; vaginal ring

1. INTRODUCTION

Approximately one million women become HIV-infected each year globally[1]. Given the role that gender-based inequities play in increasing women's vulnerability to HIV infection, researchers and advocates alike have called for the prioritization of female-controlled HIV prevention methods[2–9]. Intravaginal rings (IVR) are an ideal prevention method due to their ability to deliver drugs continuously, the possibility of coitally-independent use, and their high acceptability given their current use for family planning and menopause treatment[10–15]. Data from two recent Phase III randomized, double-blind placebo-controlled trials examining the efficacy of a dapivirine IVR as an HIV-prevention method found that women's risk of HIV-1 infection significantly decreased among dapivirine-using participants [16]. IVR efficacy, however, was dependent on participant adherence [11]. These findings highlight the importance of incorporating bio-behavioral perspectives to understand

participants' acceptability of and adherence to study products, paying close attention to how these innovative products fit (or do not fit) in women's lives.

To date, IVR acceptability and adherence research has found that women find it to be a promising method for HIV-prevention [17–21]. Among women who have used an IVR for HIV prevention in clinical trials, most have felt comfortable wearing it[13,19] and found it easy to use [20]. Across studies, women have also reported not being aware of the IVR during daily activities [13,19]. Intermittent or non-use of the IVR has been attributed to concerns of using the ring during menses, desires to clean the IVR, partial expulsions during normal activities, or requests by male partners [14,21–23]. Building on this prior work and the promise of an IVR as a new HIV prevention method, this manuscript describes the acceptability of and adherence to three new IVR formulations among U.S. women participating in the Microbicide Trials Network (MTN)-027 trial.

The MTN-027 study was a Phase I trial that sought to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of IVRs containing vicriviroc-only (VCV, MK-4176), MK-2048-only, VCV and MK-2048 (MK-2048A), and compared to placebo [24]. Both VCV and MK-2048 are highly potent antiretrovirals (ARVs)[25]. The combination of VCV and MK-2048 into an IVR is based on a strong clinical rationale for combining ARV drugs with different mechanisms of action to increase the breadth of protection and limit the emergence of resistant HIV viral strains. Thus, as a secondary objective of MTN-027, IVR acceptability was measured throughout the 28-day study period in order to examine women's experiences with IVRs containing these new drug formulations. Consistent with Morrow and Ruiz's [26] framework for microbicide acceptability research, we employed a mixed-methods approach to understand women's experiences using these IVRs after 28 days of use.

2. METHODS

Sample

Study participants were 48 female-born and female-identified adults who were randomly assigned to one of four study arms: 1) an IVR containing 182 mg VCV (MK-4176), 2) an IVR containing 30 mg MK-2048, 3) an IVR containing 182 mg VCV (MK-4176) and 30 mg MK-2048, or 4) a placebo IVR. The VCV (MK-4176) IVR is smooth, flexible and translucent with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The MK-2048 IVR is a smooth, white to off-white, opaque IVR, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The MK-2048A IVR is a smooth, white to off-white, opaque IVR, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The placebo IVR is an EVA copolymer IVR with a vinyl acetate content of 28% w/w. The placebo IVR is a smooth, flexible, translucent IVR, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

Data collection took place between June 2015 and April 2016 in Pittsburgh, PA and Birmingham, AL. Participants were recruited through family planning and gynecology clinics, colleges and universities, websites, as well as community-based organizations, word of mouth, and via street-based outreach. Some participants (n=10) were previous U.S.-based microbicide trial participants who had signed up for email notifications of future studies, or

were referred to the study from other local research projects or other health and social service providers serving the target study population.

Eligible women were 18-45 years old, HIV-negative, willing to be sexually abstinent during the trial, and using effective contraception. Major exclusion criteria included: receipt of pre- or postexposure HIV prophylaxis in past 6 months; pregnancy or breastfeeding; significant blood chemistry or hematology abnormalities; hepatitis B or C virus infection; requiring treatment for a urinary, reproductive tract, or sexually transmitted infection; and clinically apparent gynecological abnormalities, including severe pelvic organ prolapse. The study was reviewed and approved by the Institutional Review Boards at all participating institutions, and participants provided written informed consent.

Clinical Procedures

Participants were screened for eligibility prior to enrolling in the study. Participants returned to the clinic within the 45-day screening window (Day 0) where they received their IVR and were instructed to self-insert it before study personnel performed a pelvic exam to ensure proper placement and adjust it, if necessary. Participants were instructed to leave the ring inserted all day, every day, and to avoid receptive intercourse and non-study vaginal products and devices such as menstrual cups, diaphragms, contraceptive rings, vaginal medications, douches, lubricants, and sex toys. They were also instructed not to use tampons during the first week of study participation and for 24 hours prior to each clinic visit following enrollment. Participants were asked to return to the clinic the three subsequent days (Days 1, 2, and 3) after IVR insertion for specimen collection for pharmacokinetic (PK) testing. Afterward, participants returned to the clinic on a weekly basis (Day 7, 14, 21, and 28) to complete administrative, clinical, and laboratory procedures, including urine, blood, vaginal, and rectal specimen collection. After 28 days of wearing the IVR, participants returned to the clinic and clinic staff removed the IVR. Participants were followed for the three subsequent days (Days 29, 30, and 31) for specimen collection for PK testing. They returned to the clinic for a final visit on Day 35. Participant reimbursement was based on local guidelines and approved by the local IRB prior to study implementation.

Behavioral Procedures

Computer-Assisted Self-Interview (CASI)

Sociodemographic characteristics.: Participants completed a baseline CASI on Day 0 regarding their sociodemographic characteristics and prior experiences with vaginal products. Demographic questions included age, race/ethnicity, relationship status, educational attainment, and sexual orientation (see Table I). Participants were also asked if they currently had a sexual partner and whether they had used ever used a vaginal ring as a contraceptive technology.

Ring acceptability.: At their final visit on Day 35, participants completed a CASI examining their overall experiences with the ring. Overall ring acceptability (“Overall, how much did you like the ring?”) was measured on a 4-point scale (1=Dislike very much, 2=Dislike, 3=Like, 4=Like very much). We also asked participants to indicate whether their acceptability of the ring had changed since the beginning of the study (“How do you like the

ring now compared to when you started the study?"). Participants could answer with one of the following responses: "I like it MORE now than when I started the study", "I like it LESS now than when I started the study", "I like it the SAME as when I first started", and "Not applicable, I do not like the ring".

Consistent with Morrow and Ruiz's [26] framework, we also examined several domains related to participants' acceptability with study products in Phase I trials (see Table 2), including their experience using the ring, and their ease of inserting or removing the ring. These items could be answered on a 4-point scale (1=Very Difficult; 4=Very Easy). Participants also reported their comfort using the ring every day on a 4-point scale (1=Very uncomfortable; 4=Very comfortable). Participants were asked to indicate how frequently they thought about the ring being inside their body, as well as their awareness of the ring during normal day-to-day activities, using a 4-point scale (1=Never; 4=A11 of the time). Participants also were asked to indicate whether their use of menstrual products (e.g., tampons, sanitary pads, menstrual cups) changed during the 28-days of IVR use.

Future use.: Participants were asked to indicate their likelihood of using a vaginal microbicide ring in the future if it provided some protection against HIV (0=No; 1=Yes). Participants were also asked to indicate their preferred method between the ring or the male condom to prevent HIV in the future using one of the following responses: "Condom", "Ring", "Neither – I dislike both products", or "Both – 1 like both products equally". Similarly, participants were asked to indicate what they perceived was their male sexual partner's preference for a HIV prevention method using one of the following responses: "Ring", "Condom", "Neither –dislikes both products", "Both – likes both products equally", "Don't know", or "I don't have a primary partner".

In-depth Interview: After completing the exit behavioral CASI (Day 35), participants also completed an in-depth interview (IDI) conducted via webcam and phone call with MPH-level trained female interviewers, located at partner research institutions in Michigan and New York. Interviewers had prior experience conducting qualitative interviews, were trained in the study-specific procedures, and completed mock interviews prior to the start of the data collection.

A total of 47 interviews were completed (one participant did not attend the last study visit on Day 35) using a semi-structured interview guide that explored participants' general study experiences, IVR adherence, and IVR acceptability. Adherence probes focused on IVR expulsion instances, physical and emotional discomfort attributed to the IVR, and any other barriers to adherence the participant encountered. Acceptability probes explored general impressions of the IVR, perceived ease or difficulty of insertion and use, use of the IVR during menstruation, predicted comfort of vaginal sex with the IVR, discussion about the IVR with a partner, and length of time for which the participant would be willing to use the IVR. The audio portion of each interview was recorded via phone call, transcribed verbatim, de-identified, and checked for accuracy. Interviews lasted an average of 30 minutes (range = 14 to 64 minutes).

Data Analytic Strategy

We used IBM SPSS [27], version 23, to compute univariate statistics from CASI data. We also used bivariate analyses to examine whether participants' experiences with the study product differed across the four study arms. For continuous measures, we used an F-test with a Tukey pairwise comparisons post-hoc test. We used Chi-Square tests for categorical variables. As a sensitivity analysis, we also examined whether participants with prior experience using a vaginal ring (whether for contraception or as a participant in other ring trials) differed from ring-naïve participants; no differences were observed across our variables of interest (data not shown).

The research team created a codebook guided by the major areas of inquiry and common probes from the interview guide [28]. The codebook included code names, explicit definitions, and inclusion and exclusion criteria to ensure coding accuracy and facilitation of inter-coder reliability analysis. To validate and finalize the codebook, three researchers independently coded three transcripts and discussed coding discrepancies to reach consensus. The codebook was then updated as needed for clarification. Two researchers coded all 47 transcripts independently by hand and then met to discuss the codes assigned to each transcript. Coding discrepancies between researchers were resolved with input from the third researcher to reach consensus. Once consensus was reached for each transcript, the final coded transcript was entered into Dedoose [29], version 7, an online application for qualitative data analysis. For the purposes of this analysis, we used thematic analysis [28] to synthesize the five major domains explored within the IDI and posited to affect product acceptability: (1) IVR physical properties; (2) IVR insertion and removal; (3) IVR use during menses; (4) IVR movement and sensation; and (5) considerations for future use. We triangulated participants' survey and qualitative data across the five domains. Illustrative participant quotes, alongside their pseudonyms, age, and study arm, are included in italics below.

3. RESULTS

Forty-eight women enrolled in the study (see Table I for sociodemographic characteristics). Forty-seven (98%) participants completed the final exit visit on Day 35. Overall product acceptability was high (see Table II), with no differences observed between the four types of IVRs. Participants' weekly reports of adherence were high; however, over a quarter of participants reported that the IVR had partially or completely come out either once (n=12, 25.0%) or two or more times (n=2, 4.2%). Most of these expulsion events occurred in one of two situations: during their menses, or while urinating or having a bowel movement. Most participants reinserted the IVR immediately; two participants waited for their next weekly clinic appointment to have the IVR re-inserted by study personnel.

IVR properties

During the exit survey, participants were asked to rate their acceptability of the IVR since starting the study. The majority of the sample reported liking the IVR more (n=17; 36.2%) or the same amount (n=26; 55.3%) since starting the study. Participants' overall acceptability of the IVR was high (M=3.23, SD=.70), with no differences observed across study arms ($F(3, 43)=1.16$, $p=.34$).

During the IDIs, however, some participants discussed the IVR's properties – its flexibility, shape, size, and thickness – in reference to positive or negative experiences they had during the study or as suggestions for future IVR development. Participants expressed differing opinions about the IVR's flexibility: some participants wanted it to be stiffer so it would be easier to grab onto and push into place, others liked it as-is or wanted it to be more flexible to increase comfort. When asked about strategies to make IVR insertion easier, one participant responded:

> "Well they just told me to do it like you did a tampon. The ring is […] very pliable, it's kind of bendy […] – it's really thin, it's almost too pliable and too bendy […] it kind of wants to get away from you. It's not like a real good place you can grab onto it to insert it because it wiggles around because it is so pliable – which is a good thing because I didn't feel it. But when you push one side the other side moves. That's the only thing with the ring." (Raina, Age 45, MK-2048/VCV Arm)

The IVR's circular shape necessitated twisting for insertion. When asked what might make the IVR easier to insert, one participant thought an oval shape would work better:

> "[…] maybe having it more of an oval shape? But that might affect it actually staying in. But that's the only thing that I can think of It was very easy to insert […] make it so it wouldn't stick out as much, so it'd be less floppy when you're trying to insert it." (Tatiana, Age 28, MK-2048/VCV Arm)

Participants had mixed feelings about the size of the IVR. Some participants suggested increasing or decreasing the size to improve comfort or reduce the risk of accidental expulsion. Most who made suggestions about the IVR's size thought it was too big.

> "Only thing - when you make the ring, just make it a little smaller if it's possible - but I know, you know, if it's possible, just a little smaller, that's it." (Susan, Age 44, Placebo)

IVR insertion and removal

In the exit survey, most participants (n=44, 93.6%) felt comfortable with the IVR being inside their body (mean (M)=3.51, standard deviation (SD)=0.69), regardless of which IVR was assigned to them in the study ($F(3,43)=2.13$, $p=.11$). On average, participants reported that the IVR was easy to insert (M=3.64, SD=0.61); there was no mean difference in participants' perceptions of IVR insertion between the four IVRs used in the study ($F(3,43)=1.37$, $p=.26$). When asked during the IDIs about their IVR experiences, most participants reported that the IVR was easy to insert, especially if they followed the instructions provided. Some asked for assistance from study personnel with first-time insertion, or confirmation from study personnel that they had placed the IVR properly.

> "[…] from the time I inserted it, the insertion was very easy. […] like I said, I never removed it. Just put[ting] it in there was easy and once the doctor went and looked it was in place." (Lourdes, Age 37, MK-2048 IVR Arm)

IVR insertion was typically accomplished following the instructions to pinch or twist it into a figure eight to decrease the IVR's size and facilitate placement within the vagina. Participants explained that squatting or putting one leg up on a higher surface also enabled

easy insertion. Other participants reported challenges with IVR insertion. Some placed the IVR themselves, but then study personnel had to reposition it because it was improperly placed. Others described not being able to get the IVR high enough in the vaginal canal, wanting a lubricant, experiencing some initial discomfort, or needing study personnel to place the IVR after they were unable to place it themselves. A few participants noted physical limitations that made placement difficult or impossible for them: short fingers, long nails, short arms, or being overweight.

> "I felt like it was, um – just putting it in by itself was like okay but it was more difficult to get it into like the upper part of my vagina because my fingers aren't that long, so like when I had my like gynecological visit afterwards, that was when the clinician moved it further up, and like once it was there it was fine. But it was - I don't think I could have gotten it up there by myself" (Maria, Age 26, MK-2048/VCV Arm)

To ameliorate insertion issues and increase acceptability, many participants suggested providing an applicator or applicator-like device to facilitate IVR placement and enable placement deeper into the vaginal canal.

> "The only thing that comes to mind just in my experience is a lot of women have a really - or are really uncomfortable about touching themselves in that manner or having that kind of close contact […], if there was an applicator that could assist in the process I would imagine that maybe more people would be comfortable." (Josephine, Age 38, Placebo)

Removal of the IVR was scheduled for all participants on Day 28. Study personnel removed the IVR for each participant. All 48 participants had the ring in situ on Day 28. During the IDI, interviewers asked participants about their experiences with the IVR removal process, as well as whether any partial or full expulsions had occurred during the study. Participants were also asked a hypothetical question about how they would feel removing the IVR themselves.

Most participants did not experience IVR expulsion before the planned removal on Day 28. They reported that IVR removal by study personnel was easy and painless. Most responded that they would feel comfortable with self-removal if they were asked to do it; a few thought having a hook-like tool would make the task easier. Despite widespread hypothetical comfort with IVR self-removal, almost all participants indicated they would not be interested in wearing an IVR that needed to be inserted and removed frequently or daily, as the hassle of ongoing insertion and removal would be too great. When asked why it was preferable to wear the IVR every day as opposed to putting it in and taking it out frequently, one participant responded:

> "[…] Just leave it there and stay there, it's comfortable like that. Because sometimes you might not put it back in the right spot where it's supposed to go or, you know, it might be positioned in the wrong direction. I prefer it just stay in there." (Susan, Age 44, Placebo)

IVR use during menses

During the exit CASI, participants were asked whether they had managed their menstruation any differently while participating in the trial. More than half of participants in the exit survey noted that they had not changed their behaviors (n=27, 57.4%). Eleven participants reported using tampons (n=2, 4.3%) or sanitary pads (n=9, 18.8%) during the trial; six women (12.5%) reported that they stopped using tampons during the trial. Three participants (6.3%) who typically used menstrual cups to manage their menses had to switch to tampons or pads because menstrual cups were prohibited in the study protocol. There were no differences in participants' changes in menstrual products between the four arms (X^2(N=47, df=3)=2.44, p=.49).

Managing menstruation while using the IVR was difficult for participants who reported that their period started during the trial. Many voiced concerns that a tampon would displace or pull out the IVR. As a result, many participants limited or avoided tampon use during the study. For participants who did use tampons, some had no trouble, while others reported expulsions or tampon interference with the IVR.

> "[…] so when I was using a tampon, it like would get like twisted on the tampon and come out when I took out the tampon. […]I mean I work out a lot, like I have physical activity, and I didn't feel it move at all but I think my period and putting a tampon it definitely like dislodged it a little bit." (Carmen, Age 21, MK-2048/VCV Arm)

In instances where a tampon precipitated expulsion, participants were generally able to reinsert the IVR immediately. Many switched to using pads after the unintended expulsion to prevent repeat incidents, even if they strongly disliked pads.

> "[…]I had used a tampon and I had it in and then I went to go and change it and […] removed the tampon and then the ring kind of slid out with it so I washed it off and […] I just reinserted it into my vagina. And I didn't know if it was a fluke so I tried wearing a tampon again, and then the next time I had to change the tampon it happened again, and so I reinserted it, I was pretty sure that it was in the right spot, and after that, for the remainder of my period, I just used a pad, just so I wouldn't have to worry about it coming out." (Joanne, Age 24, MK-2048/VCV Arm)

A few participants disliked the menstrual cup restriction, saying they did not believe the menstrual cup would interfere with the IVR.

> "Honestly, I would be curious to try it with the Diva cup, but I was just told that I couldn't. After using tampons, I don't see why I wouldn't be able to use the Diva Cup. I would be curious to try it out. If that wasn't an option I would be fine with using tampons, I would just be very mindful when taking it out to be careful of the ring." (Maria, Age 26, MK-2048/VCV Arm)

Participants who reported extremely light or no menses during the study indicated that, hypothetically, they would be unlikely to use tampons while wearing the IVR if they were bleeding heavily. These hypothetical statements were made both in reference to themselves and other women who might use the IVR, and primarily revolved around a fear of IVR

expulsion. Two participants asserted they would be willing to be uncomfortable or change their menstruation management routine if the IVR offered them protection from HIV.

IVR movement and sensation

During the exit survey, participants reported how often they thought about the IVR inside their bodies. Most participants did not think about the IVR at all (n=19, 40.4%) or only some of the time (n=24, 50%); four participants reported thinking about the IVR often (8.3%). There were no differences by study arms (X^2(N=47, df=6)=9.31, p=.16). Participants were also asked how often they were aware of the IVR while doing normal daily activities. Most participants reported being unaware that the IVR was present during normal daily activities (never: n=29, 61.7%; sometimes: n=17, 36.2%); one participant reported frequent awareness of the IVR's presence during daily activities (n=1, 2.1%). There were no differences by study arms (X^2(N=47, df=6)=7.08, p=.31).

In the IDIs, some participants stated that the IVR remained in place from the moment it was inserted to when it was removed, and was undetectable throughout.

> "[…] it didn't require anything of me; it was very easy, I just put it in and forgot about it. And you know, it wasn't problematic, it wasn't slipping and moving and you know, I didn't think about it." (Lillie, Age 34, MK-2048/VCV Arm)

Participants who discussed unpleasant sensations from the IVR typically experienced these feelings if the IVR moved or slipped down towards the vaginal opening. The discomfort was resolved by repositioning the IVR to sit higher in their vaginal canal.

> "[…] my ring […] wouldn't stay in the right position […] I just felt like it was going to come out and so I would check on it a lot, and I would try to reposition it and up - you know higher up and I really couldn't get it where it needed to be. […] And it never came out on its own, it was never out, but it was very close to, like the entrance […]" (Emily, Age 28, VCV Arm)

IVR movement without expulsion was commonly reported by participants when they were menstruating or using the bathroom. In addition to IVR expulsions during menses, some participants reported IVR expulsions in the bathroom - either during urination or a bowel movement. Though actual expulsion in the bathroom was not often reported, participants' concern about this scenario was more widespread.

Future Use of the IVR and its Implications for Sexual Behavior

The study protocol mandated abstinence during the trial, so the exit survey and IDI asked participants to imagine how they would feel about having sex with the IVR. In the exit survey, when given the option of choosing between an IVR or a male condom as a HIV prevention method, most participants reported preferring an IVR (n=29, 63.0%) over a male condom. Over a quarter of the sample reported liking the methods equally (n=12, 26.1%). The remaining five participants reported preferring a condom (n=4, 8.7%) or disliking both methods (n=1, 2.2%). There were no differences observed by study arm (X^2(N=47, df=9)=7.90, p=.54).

The exit survey also asked which HIV prevention method participants thought their male partners would prefer (choosing between the IVR and a male condom), with no differences observed by study arm (X^2(N=47, df=9)=10.19, p=.34). A large proportion of participants reported believing that their partners would prefer the IVR (n=20, 43.5%) over a condom or would like both methods equally (n=2, 4.3%). Of the remaining participants, however, many stated they couldn't predict their partners' preferences (n=13, 28.3%) or they were unable to answer the question given they did not have a partner at that time (n=11, 23.9%).

The majority of participants (n=38, 80.9%) reported they would use an IVR similar to the one used in the trial for HIV prevention in the future; no differences between study arms were observed X^2(N=47, df=3)=.61, p=.89). During the IDIs, most participants said they would be comfortable having sex while wearing the IVR, but a few voiced hypothetical concerns that could impact their decision to use the IVR. These potential barriers included concerns that the IVR would move into an undesired location or get lost within the vagina during or after sex, and concerns that their male partners would experience discomfort from the IVR. These potential issues made a few participants unwilling to envision having sex with the IVR.

> "[…] I just would be scared that he may push the ring too far […] I know it can't get lost in your body, but I don't want anything wedged anywhere." (Eleanor, Age 28, Placebo)

During the IDIs, most participants voiced a willingness to have sex with the IVR if they and their partners did not experience any unpleasant sensations and the IVR remained in their vagina. These findings align with data from the exit surveys.

> "I think that because of the position of where it was, if it was comfortable, I don't think during sex it could really pose a problem for the female or the male." (Monica, Age 41, MK-2048 IVR Arm)

Participants who were concerned about their partners' reactions to having sex with the IVR thought that women should be educated on effective communication strategies to negotiate IVR use in these situations.

> "[…] I think educating women on how to talk to their partners. I think there are probably plenty of women who might not be comfortable having the conversation with their partner about what they could do as a couple." (Josephine, Age 38, Placebo)

4. DISCUSSION

Although a dapivirine IVR has been found to be efficacious in prevention HIV [10], researchers have continued to explore whether other ARVs could serve as a microbicide agent [30]. MTN-027 examined three potential microbicide rings containing vicriviroc, MK-2048, or a combination of vicriviroc and MK-2048, as well as a placebo ring. Findings [24] from the MTN-027 parent trial found that all three IVRs being tested were deemed safe, with most women being fully adherent across the 28-day trial [24]. In order to supplement the parent trial's findings and given the use of three new drug formulations in these IVRs, we

employed a mixed-methods analysis to understand participants' acceptability of and adherence to the three IVRs.

Overall, participants' acceptability of the IVRs under study was high, with no detectable differences observed between the arms. During the IDIs, many participants discussed how the IVRs' physical characteristics affected their use of the product throughout the study. Consistent with prior IVR trials [14,19], most participants did not experience any difficulties inserting or removing the IVRs, were comfortable with the ring inside their bodies, and were not aware of the ring's movement during day-to-day activities. Moreover, most participants reported that they would prefer an IVR to male condoms as an HIV prevention method, corroborating prior evidence [2,13,14,19,21] indicating women's desire and willingness for a female-controlled HIV prevention method.

Consistent with prior studies [14,19,31], some participants experienced involuntary expulsions during their daily activities and/or their menstrual cycle. In most cases, participants felt comfortable re-inserting the IVR when this occurred. To circumvent these problems, some participants changed their preferred menstruation management product (e.g., from tampon to pads) to circumvent involuntary expulsions of the ring. In addition, several participants had to change their preferred menstruation management product (e.g., menstrual cup) to adhere to the protocol requirements. Strategies to support women's use of an IVR during menses will be needed as IVRs are tested and rolled-out across diverse cultural contexts where different menstrual products (e.g., tampons, menstrual cups) may be available, supported, or discouraged. In a recent global scoping review examining women's responses to changes in their menstruation as a result of their contraceptive use, Polis and colleagues [32] noted that changes were a significant and underappreciated component of product discontinuation. Building on lessons learned from the contraceptive literature, the collective findings regarding IVR use during menstruation suggest that future IVR trials examining long-term patterns of acceptability and adherence should consider optimal behavioral congruence between women's IVR use and and menstruation management.

Women participating in the trial were asked to be sexually abstinent during the 28 days of IVR use. As a result, we have no data to understand participants' acceptability of the IVR during sexual intercourse or to examine whether sexual behaviors affect adherence to the IVR. Even in the absence of sexual behavior, however, participants foreshadowed hypothetical events that would deter them from using the IVR during sex. Women expressed concern that the IVR would be hard to remove if it shifted during sex or that their partners would disapprove of their use of the IVR. Albeit hypothetical, women voiced the importance of being educated on effective communication strategies to manage these concerns. These findings are consistent with prior IVR research in sub-Saharan Africa, in which women described how their sexual experiences with the IVR were affected by their partners' reactions to the IVR, anticipations of their partners' reactions, and their decision whether to disclose IVR use to their partner [21]. Building on these prior findings, our analysis reinforces the need to explore women's anticipated and actual experiences using IVRs during sex, as well as their discussions with partners about their IVR use, given the influence of sexual behavior on women's acceptability of and adherence to the ring [20,26,33]. interventions

designed to strengthen women's self-efficacy and skills to negotiate IVR use with their sexual partners may be warranted as an effective HIV prevention IVR is rolled out.

Several limitations to this study deserve mention. First, given the nature of this Phase I safety trial, we recruited a small sample of low-risk women to participate in this study. Women living in vulnerable, high-risk contexts may have different needs and perceptions of the IVRs under study. Second, a subsample of participants had prior experiences with IVRs, either because a vaginal ring was their preferred contraceptive method and/or because they had previously participated in microbicide trials. Although their overall acceptability and adherence of a vaginal ring might differ from that of peers who have never used the ring in the past, we found no differences based on prior ring use in their bivariate analyses. Nonetheless, future research should remain vigilant to this possibility, and examine whether IVR acceptability and adherence differs based on women's prior experiences with various contraceptive technologies. Third, participants' social desirability regarding the IVR's acceptability may have influenced their responses during the in-depth interviews; however, the convergence between their CASI self-reports and their discussions with the interviewers do not support this claim. Fourth, our participants' acceptability of and adherence to the IVR may not be generalizable to other microbicide IVR candidates or to women living in other cultural contexts. Future research examining IVR acceptability and adherence remains vital as new ARV drugs and devices are tested as potential HIV prevention methods.

Participants' positive experiences with the IVRs tested in this trial are encouraging. Although participants expressed some minor concerns about the IVR, most women reported that they would prefer to use an efficacious microbicide IVR over a male condom for HIV prevention if it were available. Moreover, our findings align with prior dapivirine-based acceptability studies, corroborating the importance of monitoring and understanding women's acceptability of the IVR in order to promote optimal adherence in the future. Future clinical trials should continue to evaluate whether women's IVR acceptability may vary based on their individual and sociocultural contexts. Additional biobehavioral research examining IVRs as a potential HIV prevention method is warranted.

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Table I.

Baseline sociodemographic characteristics of study sample (N=48)

Variable	M (SD)/N (%)
Age (years)	30.7 (6.9)
Race/Ethnicity	
Non-Hispanic Black/African American	18 (37.5%)
Non-Hispanic White	26 (54.2%)
Hispanic/Latina White	1 (2.1%)
Biracial	2 (4.1%)
Native American/Alaskan Native	1 (2.1%)
Relationship Status	
Single	17 (35.4%)
In a Relationship	19 (39.6%)
Married	12 (25.0%)
Educational Attainment	
Partial College	14 (29.2%)
College Graduate	15 (31.3%)
Partial Graduate School	9 (18.8%)
Graduate School Degree	10 (20.8%)
Sexual Orientation	
Heterosexual	38 (79.2%)
Bisexual	4 (8.3%)
Lesbian/Homosexual	4 (8.3%)
Queer	2 (4.2%)
Has a sex partner	30 (62.5%)
Prior history using a vaginal ring for contraception	10 (20.8%)

Table II.

Women's product acceptability and IVR-related behaviors as reported on Day 35 on Exit Visit CASI Survey (N=47)

Variable	Range	Overall N=47	Arm 1 (VCV IVR) n=11	Arm 2 (Placebo) n=12	Arm 3 (MK-2048 IVR) n=12	Arm 4 (MK-2048A combo IVR) n=12
Overall, how easy or difficult was it to use the ring	1 (Very Difficult) – 4 (Very Easy)	3.64 (0.61)	3.36 (0.67)	3.83 (0.39)	3.75 (0.45)	3.58 (0.79)
How difficult or easy was it to insert the ring?	1 (Very Difficult) – 4 (Very Easy)	3.41 (0.79)	3.27 (0.65)	3.64 (0.51)	3.64 (0.67)	3.09 (1.14)
How often did you think about the ring being inside your body?	1 (Never) - 4 (All of the time)	1.68 (0.63)	1.91 (0.54)	1.42 (0.52)	1.83 (0.58)	1.58 (0.79)
How often were you aware of the ring during your normal daily activities?	1 (Never) - 4 (All of the time)	1.40 (0.54)	1.73 (0.65)	1.25 (0.45)	1.42 (0.52)	1.25 (0.45)
Overall, how did it feel to have the ring inside you every day?	1 (Very Uncomforta ble) – 4 (Very Comfortable)	3.51 (0.69)	3.27 (0.65)	3.75 (0.45)	3.25 (0.87)	3.75 (0.62)

Statistics reported as mean (standard deviation). There were no significant differences between study arms.