JOURNAL OF WOMEN'S HEALTH
Volume 31, Number 7, 2022
Mary Ann Liebert, Inc.
DOI: 10.1089/jwh.2021.0121

Open camera or QR reader and scan code to access this article and other resources online.

# Acceptability and Preference for 3-Month Versus 1-Month Vaginal Rings for HIV-1 Risk Reduction Among Participants in a Phase 1 Trial

Sarah T. Roberts, PhD,[1] Imogen Hawley, MSc,[1] Ellen Luecke, MPH,[1] Barbara Mensch, PhD,[2] Theresa Wagner, MPH,[3] Craig Hoesley, MD,[4] Tara McClure, MPH,[5] Clara P. Dominguez Islas, PhD,[6] Jeanna M. Piper, MD,[7] Albert Y. Liu, MD,[3,8] and Ariane van der Straten, PhD[1,8,*];
and on behalf of the MTN-036/IPM 047 Protocol Team for the Microbicide Trials Network

## Abstract

***Background:*** The monthly dapivirine vaginal ring provides partial protection against HIV, and a longer duration ring may reduce user burden and improve adherence. We examined acceptability and preference for 3-month versus 1-month rings for HIV-1 risk reduction in a phase 1 clinical trial.
***Materials and Methods:*** In Microbicide Trials Network-036/International Partnership for Microbicides 047, 49 HIV-negative participants aged 18–45 were randomized to one of two 3-month rings or the 1-month ring. Acceptability ratings were collected at enrollment, week 4, and study exit (week 13). At exit, ring preference was assessed quantitatively among all participants and a randomly selected subset of 24 participants completed in-depth interviews. Quantitative and qualitative findings were integrated to explore factors influencing acceptability and preference.
***Results:*** Acceptability of each ring was initially moderate and increased during the trial. Ratings were lower in the 3-month ring arms than the 1-month arm at each time point, including baseline. Most participants (34/47; 72%) preferred a 3-month ring at exit; however, this proportion was significantly lower within some subgroups characterized by site, education, race/ethnicity, and experiences with ring use. Qualitative interviews revealed reservations about hygiene and safety of the 3-month ring, including discomfort with use during menses, but these were usually outweighed by its increased convenience.
***Conclusions:*** Both ring durations were highly acceptable at study exit. Although most participants preferred a 3-month ring, preference was more divided in certain subgroups, highlighting the benefit of offering different duration options. Providing additional support to address concerns about hygiene and safety may improve acceptability of a 3-month vaginal ring.

**Keywords:** vaginal rings, dapivirine, HIV prevention, acceptability, preference

[1]Women's Global Health Imperative (WGHI), RTI International, Berkeley, California, USA.
[2]Population Council, New York, New York, USA.
[3]Bridge HIV, San Francisco Department of Public Health, San Francisco, California, USA.
[4]Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama, USA.
[5]FHI360, Durham, North Carolina, USA.
[6]Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.
[7]Division of AIDS, National Institutes of Health, Bethesda, Maryland, USA.
[8]Department of Medicine, University of California San Francisco, San Francisco, California, USA.
**Current affiliations:* ASTRA Consulting (Kensington, California, USA) and University of California San Francisco.

## Introduction

HIV continues to disproportionately impact women and girls in sub-Saharan Africa, and despite ongoing progress in fighting the epidemic, there were 1.7 million new infections worldwide in 2019.[1] A monthly vaginal ring containing the antiretroviral dapivirine (DPV) reduced HIV risk by 27%–35% among women in two randomized, double-blind, placebo-controlled phase 3 trials[2,3] and more so in two open-label extension studies.[4,5] The European Medicines Agency recently adopted a positive scientific opinion on this ring for use by women in low- and middle-income countries,[6] which is expected to facilitate approval by national regulatory authorities in sub-Saharan Africa, and Food and Drug Administration (FDA) submission is underway.

As with oral pre-exposure prophylaxis, the effectiveness of the ring depends on adherence.[7] Lessons from contraceptive research suggest that longer duration methods are more acceptable and have higher continuation rates and lower rates of user error, leading to more effective prevention of unwanted pregnancies.[8–10] Similarly, an extended duration HIV prevention ring, such as one replaced quarterly instead of monthly, may reduce user burden, simplify use, and reduce cost and burden on the health care systems, thus increasing access, acceptability, adherence, and ultimately public health impact.

However, higher acceptability is not a foregone conclusion: participants in formative studies have raised concerns about hygiene and comfort of a longer-duration ring, especially when worn during menses.[11–13] In a recent phase 1 study conducted in the United States, two extended duration DPV vaginal rings, used over 13 weeks, were found to be well tolerated and to have a similar safety profile as the monthly ring.[14] In this article, we compare acceptability of and stated preference for the 3-month versus 1-month rings in that study.

## Materials and Methods

### Study design

Microbicide Trials Network (MTN)-036/International Partnership for Microbicides (IPM) 047 was a phase 1, randomized, three-arm trial conducted at two clinical research sites in Birmingham, AL and San Francisco, CA between November 2017 and January 2019 (clinical trial no. NCT03234400). The design, procedures, and primary findings have been previously published.[14] Briefly, 49 participants were enrolled and randomized (1:1:1) to receive a silicone elastomer vaginal ring containing either 25, 100, or 200 mg DPV, all visually identical. Eligibility criteria included being born female, aged 18–45 years, HIV-uninfected, and generally healthy; willing to refrain from inserting any non-study vaginal products or objects (except tampons) into the vagina for the duration of study participation; not pregnant or breastfeeding; and having regular menstrual cycles or using a method of contraception for which the absence of regular menstrual cycles is an expected, normal consequence (*i.e.,* a progestin-only method or continuous combination oral contraceptive pills). There were no criteria related to sexual orientation or sexual behavior. The 25 mg ring was replaced every 4 weeks for 8 weeks and then worn for the remaining 5 weeks until study exit. The 100 and 200 mg rings were worn continuously for 13 weeks, and participants were blinded to their assigned dosage. All participants, regardless of ring assignment, were instructed to wear the ring continuously for the designated duration, including during menses.

### Procedures for data collection

Quantitative. Behavioral data were collected *via* a computer-assisted self-interview at enrollment, day 28, and day 91 (study exit). Topics included demographics, vaginal and sexual practices, sexual partners, ring acceptability, and, at exit only, ring preference. This analysis used measures of overall acceptability (how much they liked the ring overall), two specific acceptability components that we hypothesized would be impacted by ring duration (use attributes such as ease of use, comfort, pain, and discomfort; and effects on sexual encounters including whether they felt the ring during sex and minded wearing the ring during sex),[15] and stated preference for a ring that can be worn for 3 months before replacement or a ring that must be replaced monthly. Detailed questions and response options are provided in Supplementary Table S1). Because participants used either a 3-month ring or a 1-month ring throughout the study, and did not have the opportunity to try both products, stated preference should be interpreted as narrowly pertaining to ring duration and not to other characteristics that could differ between the study rings (*e.g.,* side effects).

Qualitative. Twenty-four in-depth interviews (IDIs) were conducted with a randomly selected subset of participants (11 in Birmingham and 13 in San Francisco) who reported engaging in penile–vaginal sex in the year before enrollment. To achieve this sample size, based on expected rates of refusal and ineligibility in prior studies at each site, 36 participants were randomized to IDIs. Randomization was stratified by study site and ring assignment. At enrollment, study staff determined whether the participant had been randomized to the IDI, and they then reviewed the behavioral data to determine eligibility. Twenty-six of the 36 randomized participants were eligible and invited to the interview, and 24 agreed to participate.

The IDIs were conducted in English by one of two trained female interviewers by using a semi-structured guide *via* video call during the day 91 visit or shortly thereafter. Topics included acceptability of assigned ring; disclosure of ring use; experience using the ring during sex or menses; and preferences for ring use durations. Interviewers documented brief summaries of each IDI within 1 day. All IDIs were audio recorded and transcribed, with transcripts reviewed for quality by interviewers and qualitative analysts.

### Analysis

Quantitative. Because we sought to evaluate the impact of ring duration on acceptability and preference, we combined the two 3-month arms (100 mg DPV ring and 200 mg DPV ring) and compared participants by assigned ring duration (1-month group vs. 3-month group). We summarized sociodemographic characteristics and sexual behavior of the study participants at baseline for the entire sample and by assigned ring duration.

Overall acceptability ratings were analyzed continuously. We calculated the median rating, interquartile range (IQR), mean, and standard deviation (SD) at each time point and tested for differences in ratings by assigned ring duration

using linear regression with robust standard errors. Models for day 28 and 91 measures included adjustment for baseline rating. We further evaluated differences in acceptability by summarizing categorical responses for each acceptability attribute at day 91, after all participants had experienced at least one full cycle of ring use, and testing for differences by assigned ring duration using Fisher's exact tests.

We evaluated three categories of participant characteristics potentially associated with stated preference for a 3-month ring over a 1-month ring: sociodemographic characteristics, sexual behavior, and experiences with ring use. The proportion of participants preferring a 3-month ring was summarized overall and by each hypothesized correlate, and 95% confidence intervals (CIs) were calculated by using the logit method. We tested for differences in preference by each correlate individually using Fisher's exact tests; we did not conduct multivariable analyses due to the small sample size. The comparison group combined participants who preferred a 1-month ring or stated no preference, due to the small number of responses in these categories.

Qualitative. Data were analyzed thematically. A codebook was developed iteratively through an inductive and deductive process based on the IDI guides and summaries. Transcripts were coded by using Dedoose software v7.0.23 by a team of four analysts (including the two interviewers and the lead author); the intercoder reliability score (pooled Cohen's kappa) for nine key codes was 0.77, indicating ''substantial'' agreement.[16] For this analysis, we generated code reports with the ''1–3 month'' code, which was applied to any discussions or comments about products used for a month to 3 months, and specifically to discussions or comments that compared the monthly and extended duration rings. Data were stratified by assigned ring duration and summarized into analytical memos. Weekly meetings were held during the analysis to discuss coding disagreements, which were resolved by consensus, and to discuss emerging themes and similarities or differences by assigned ring duration. Subsequently, to explore differing themes in the qualitative and quantitative results, a participant-level analysis was conducted to synthesize quantitative acceptability ratings and preferences, excerpts from the analysis memos, and additional code reports for the ''menses'' and ''side effects'' codes. Direct quotations, included to illustrate key themes, are indicated by italic text and accompanied by the participant's assigned ring duration, study site, and acceptability rating and stated preference at study exit.

### *Ethics statement*

The study protocol was approved by the Institutional Review Board at each site and was overseen by the Division of AIDS (DAIDS) and MTN. All participants provided written informed consent before study participation.

## Results

### *Participant characteristics*

Table 1 shows baseline participant characteristics stratified by assigned ring duration (1-month vs. 3-month rings). The two groups were similar overall, with no statistically significant differences. However, participants in the 3-month ring group were more likely to be college graduates than those in the 1-month ring group (59% vs. 41%), and they were less likely to have previously used a vaginal ring (16% vs. 35%) but more likely to have previously used a cervical barrier or menstrual cup (16% vs. 6%). The subset of IDI participants were similar to the overall study population on all measures, except that they were less likely to be non-Hispanic Caucasian (33% vs. 40%) or African American (29% vs. 52%) and more likely to be Hispanic or ''Other'' (38% vs. 8%, $p$ for all race/ethnicity categories = 0.038), and they were more likely to have a current sex partner (83% vs. 52%, $p = 0.032$) due to the inclusion criterion of having had penile–vaginal sex in the past year.

### *Acceptability*

Figure 1 shows median ring acceptability ratings throughout the study. At baseline, ratings were significantly higher among participants assigned to the 1-month ring (median [IQR] 5 [5–7], mean [SD] 6.2 [1.8]) than those assigned to the 3-month rings (median [IQR] 5 [5–5], mean [SD] 5.2 [0.9]; $p = 0.03$), despite the fact that data were collected before randomization and did not specify the ring duration. Ring acceptability increased in both groups during the trial but remained significantly higher in the 1-month ring group at each time point, even after adjusting for baseline rating. The largest difference was at day 28, when median ratings increased to 10 in the 1-month ring group (IQR 8–10, mean [SD] 8.8 [1.8]) but remained at 5 in the 3-month ring group (IQR 5–8.5, mean [SD] 6.7 [2.1]; $p = 0.004$). By day 91, median ratings increased to 8 (IQR 5–9, mean [SD] 7.4 [2.0]) in the 3-month ring group and remained at 10 in the 1-month ring group (IQR 8–10, mean [SD] 8.9 [1.5]; $p = 0.04$).

Participants rated both rings highly on most specific acceptability components at day 91 (Table 2). More than 90% reported that the ring was easy or very easy to use, comfortable or very comfortable, and did not cause worries, fear, or other emotional discomfort. Less than 1/3 reported checking that the ring was still inside the vagina more than once or twice, experiencing pain or physical discomfort, or worrying about the ring being dirty or hygienic, whereas 45% reported at least some worry about the ring causing long-term health problems. Twenty-five participants (51%) were not bothered at all by wearing the ring during menses, 9 (17%) were bothered to some degree, and 15 (31%) reported never wearing the ring during menses. The latter group primarily consisted of participants whose menses were suppressed due to their contraceptive method; only one reported removing the ring due to menses. Of the participants who had worn the ring during sex, most (51%) never felt it and only 3 (6%) minded the experience.

The 1-month ring received higher ratings in most categories, but only two differences were statistically significant: 1-month ring users were more likely to never have checked whether the ring was still in place during the course of the study (76% vs. 41%, $p = 0.03$), and only 6% of 1-month ring users reported experiencing a change in the vaginal environment that bothered them, compared with 47% of 3-month ring users ($p < 0.001$). The most common changes that bothered participants using the 3-month rings were the vagina being wetter ($n = 7$) or having a change in odor ($n = 10$).

Table 1. Baseline Characteristics

| | *1-month ring* | *3-month rings* | *Overall* | p[a] |
|---|---|---|---|---|
| Total (*n*) | 17 | 32 | 49 | — |
| Age, median (IQR) | 29 (27–34) | 29.5 (25.5–35) | 29 (26–34) | 0.85 |
| | n *(%)* | n *(%)* | n *(%)* | |
| Race/ethnicity | | | | 0.44 |
| Non-Hispanic Caucasian | 7 (41) | 11 (34) | 18 (37) | |
| African American | 8 (47) | 12 (38 | 20 (41) | |
| Other[b] | 2 (12) | 9 (28) | 11 (22) | |
| Study site | | | | >0.99 |
| San Francisco, CA | 8 (47) | 16 (50) | 24 (49) | |
| Birmingham, AL | 9 (53) | 16 (50) | 25 (51) | |
| College graduate | 7 (41) | 22 (59) | 29 (59) | 0.08 |
| Currently engaged in paid work | 14 (82) | 24 (75) | 38 (78) | 0.73 |
| Currently a student | 4 (24) | 8 (25) | 12 (25) | >0.99 |
| Sexual orientation | | | | 0.63 |
| Heterosexual | 10 (59) | 17 (53) | 27 (55) | |
| Lesbian | 2 (12) | 4 (13) | 6 (12) | |
| Bisexual | 3 (18) | 3 (9) | 6 (12) | |
| Queer | 2 (12) | 8 (25) | 10 (20) | |
| Nulliparous | 11 (65) | 22 (69) | 33 (67) | >0.99 |
| Any past vaginal ring use (*e.g.,* NuvaRing, Estring, Femring) | 6 (35) | 5 (16) | 11 (23) | 0.16 |
| Any past cervical barrier or menstrual cup use | 1 (6) | 5 (16) | 6 (12) | 0.65 |
| Any penile–vaginal sex in the past 12 months | 13 (76) | 23 (72) | 36 (73) | 0.50 |
| Currently has a primary sex partner | 12 (71) | 21 (66) | 33 (67) | >0.99 |
| Gender of current primary sex partner | | | | 0.61 |
| Man | 10 (83) | 19 (91) | 29 (88) | |
| Woman | 2 (17) | 2 (10) | 5 (12) | |
| Any past oral PrEP use | 0 (0) | 1 (3) | 1 (2) | >0.99 |

[a]*p*-Values obtained from Wilcoxon rank sum (for age) and Fisher's exact tests (all other variables).
[b]Includes five Latina/Hispanic participants.
IQR, interquartile range; PrEP, pre-exposure prophylaxis.

### *Preference*

At study exit, 34 participants (72%, 95% CI 58%–83%) stated preference for a 3-month duration ring, whereas 6 (13%) preferred a 1-month ring and 7 (15%) had no preference (Fig. 2). Participants were more likely to prefer a 3-month ring if they were from the San Francisco versus Birmingham site (87% vs. 47%, $p=0.049$) and if they were college graduates (89% vs. 47% among non-graduates, $p=0.003$); African American participants were less likely to prefer a 3-month ring (50%), compared with non-Hispanic Caucasians (88%) and those in the ''Other'' category (91%,

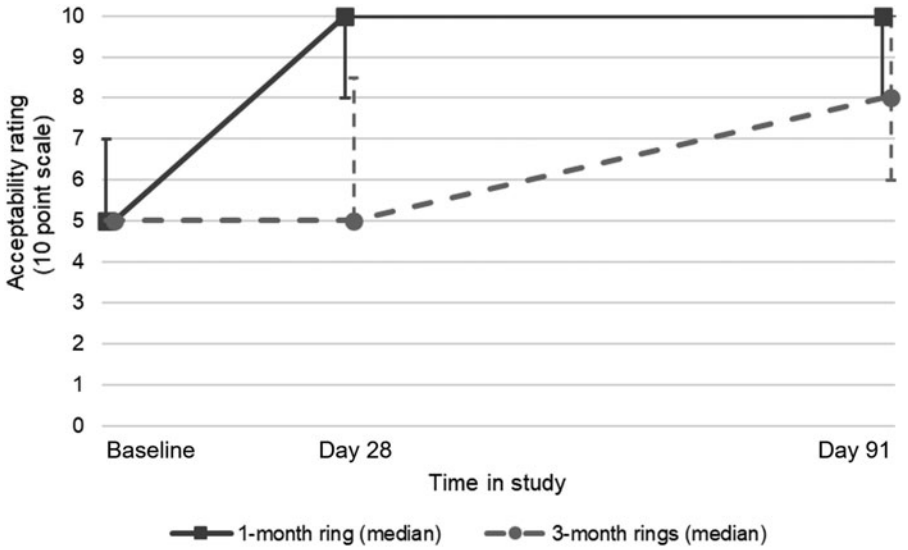


**FIG. 1.** Overall acceptability ratings by study visit. Error bars show IQR. When one side is not visible, the value is the same as the median. IQR, interquartile range.

Table 2. Specific Components of Acceptability at Day 91, by Assigned Ring Duration

| | *1-month ring* n *(%)* | *3-month rings* n *(%)* | *Overall* n *(%)* | p[a] |
|---|---|---|---|---|
| Total | 15 (100) | 32 (100) | 49 (100) | |
| Overall ease of ring use | | | | 0.50 |
| Very easy | 13 (87) | 25 (78) | 38 (81) | |
| Easy | 1 (7) | 6 (19) | 7 (15) | |
| Difficult | 1 (7) | 1 (3) | 2 (4) | |
| Very difficult | 0 (0) | 0 (0) | 0 (0) | |
| How it felt to have the ring inside them every day | | | | 0.27 |
| Very comfortable | 11 (73) | 21 (66) | 32 (68) | |
| Comfortable | 3 (20) | 11 (34) | 14 (30) | |
| Uncomfortable | 0 (0) | 0 (0) | 0 (0) | |
| Very uncomfortable | 1 (7) | - | 1 (2) | |
| How often they checked whether the ring was still inside | | | | **0.03** |
| Never | 13 (76) | 13 (41) | 26 (53) | |
| Once or twice | 1 (6) | 12 (38) | 13 (27) | |
| More than once or twice[b] | 3 (18) | 7 (22) | 10 (20) | |
| Any change in vagina while wearing the ring and how much the change bothered them | | | | **0.001** |
| Change in vagina: did not bother at all | 7 (41) | 2 (6) | 9 (18) | |
| Change in vagina, bothered a little, somewhat, or very much | 1 (6) | 15 (47) | 16 (33) | |
| No change in vagina | 9 (53) | 15 (47) | 24 (49) | |
| Ring caused emotional discomfort[c] | 1 (6) | 3 (9) | 4 (8) | > 0.99 |
| Ring caused pain or physical discomfort | 2 (12) | 8 (25) | 10 (20) | 0.46 |
| Worry about the ring being dirty or unhygienic | | | | 0.67 |
| Not at all | 11 (73) | 21 (66) | 32 (68) | |
| A little | 4 (27) | 8 (25) | 12 (26) | |
| Somewhat or very much | 0 (0) | 3 (9) | 3 (6) | |
| Worry about the ring causing infection, infertility, or other long-term health problems | | | | 0.24 |
| Not at all | 6 (40) | 20 (63) | 26 (55) | |
| A little | 7 (47) | 7 (22) | 14 (30) | |
| Somewhat or very much | 2 (13) | 5 (16) | 7 (15) | |
| Bothered by wearing the ring during menses | | | | 0.44 |
| Not at all | 11 (65) | 14 (44) | 25 (51) | |
| Any response > not at all[d] | 2 (12) | 7 (22) | 9 (18) | |
| Did not wear ring during menses | 4 (24) | 11 (34) | 15 (31) | |
| How often they felt the ring during sex | | | | 0.78 |
| Never | 9 (60) | 15 (47) | 24 (51) | |
| Some, most, or all of the time | 3 (20) | 7 (23) | 10 (21) | |
| Never had sex with ring in | 3 (20) | 10 (31) | 13 (28) | |
| Minded wearing the ring during sex | | | | 0.41 |
| Yes | 0 (0) | 3 (9) | 3 (6) | |
| No | 12 (80) | 19 (59) | 31 (66) | |
| Never had sex with ring in | 3 (20) | 10 (31) | 13 (28) | |

Bold font indicates $p<0.05$.
[a]$p$-values obtained from Fisher's exact tests.
[b]All responses were ''once a week or less.''
[c]All responses were ''once or twice'' or ''once a week or less.''
[d]Response >1 on the visual analog scale.

$p=0.017$). The proportion who preferred a 3-month ring was also lower among participants who checked that the ring was in place more than once or twice during the study (40%) compared with checking once or twice only (85%) or never (79%, $p=0.049$), as well as those who were bothered by wearing the ring during menses (45%) compared with not being bothered at all (73%) or not wearing the ring during menses (93%, $p=0.029$). Stated ring duration preference was not associated with assigned ring duration, age, sexual orientation, prior ring experience, sexual behavior or partnership status, or additional measures of ring acceptability (see Supplementary Table S2 for full results).

### *Qualitative insights*

Nearly all IDI participants liked their rings and found them easy to use. Preference for the 3-month ring was predominant and largely driven by its greater convenience, which had

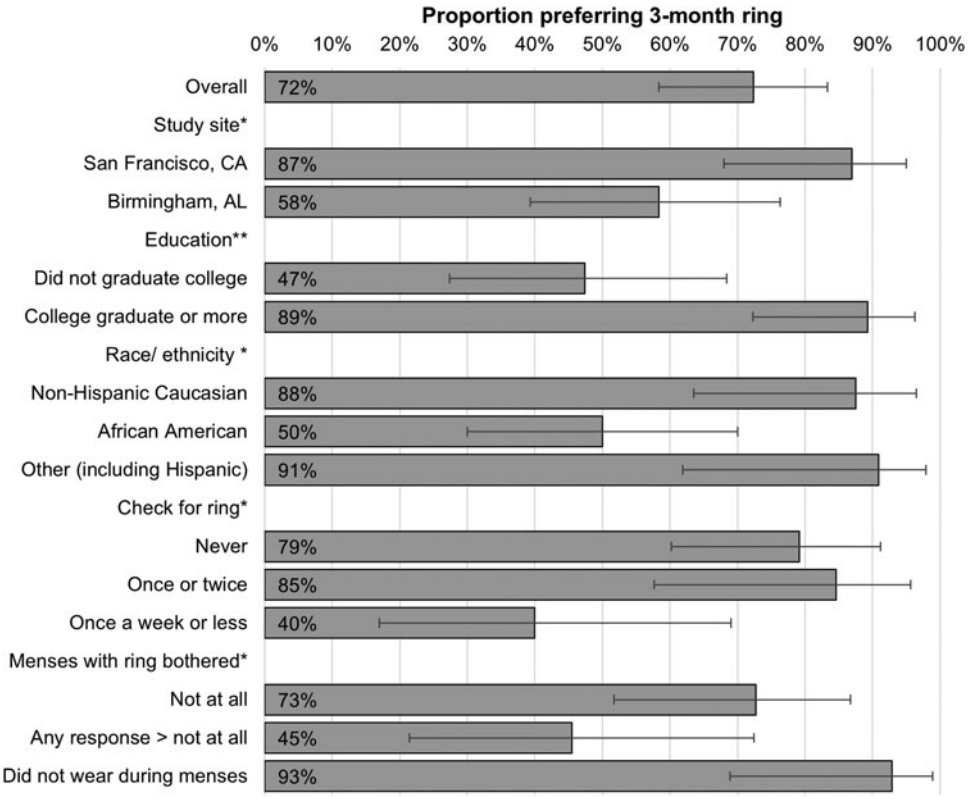


**FIG. 2.** Correlates of stated preference for a 3-month ring at day 91/study exit. $*p<0.05$; $**p<0.01$. $p$-Values obtained from Fisher's exact tests. Error bars show 95% CIs. CI, confidence interval.

three key dimensions (see Table 3 for illustrative quotes). First, participants felt an extended duration ring required less thought and attention than a 1-month ring. Participants described their busy lifestyles to illustrate the burden of replacing a ring and their overall preference for a ring that causes less disruption to daily life. Specifically, being able to ''forget'' about the ring for a longer period of time was seen as an advantage. Second, the removal and reinsertion of a new ring was burdensome for some participants, and they appreciated that the longer regimen required these procedures less often. Third, although all study participants were required to adhere to the same visit schedule regardless of assigned ring duration, several participants imagined that outside of a clinical trial it would be more convenient to have an extended duration ring to reduce the number of clinic or pharmacy visits.

Despite this preference, there were three main issues that contributed to lower acceptability of a 3-month ring, including skepticism about the hygiene and safety of a 3-month ring, discomfort with using the ring during menses, and perceived side effects. In most cases, these issues were outweighed by the convenience of the 3-month ring, but occasionally they led participants to prefer the 1-month ring or to express ambivalence.

Most participants described concerns that leaving a ring in for 3 months could make them unclean or increase the risk of vaginal infections (Table 4, Theme A). These concerns were cited both by participants who had used this ring during the study and by 1-month ring users when asked about their interest in a longer duration ring. Several participants in the 3-month ring group said they would like to have

Table 3. Illustrative Quotes on Convenience of a 3-Month Ring

| *Theme* | *Illustrative Quotes* |
|---|---|
| Less disruption to busy lives | ''I would pick the three month because, like I said, that's, for me it's one less thing to do. So the longer I can wear it safely, the more I would want the longer one because people are just too busy. You know, so I don't want to have to remember every month to go change this out…'' 3-month ring, Birmingham, Rating: 10, Prefers 3-month ring |
| Less burden of insertion and removal | ''I wanted the smaller dosage because I thought it would be healthier and there would be no issues of cleanliness or anything like that, but then once I struggled to put it in I was like, 'I'm, I'm glad I got the thirteen week.''' 3-month ring, Birmingham, Rating: 5, Prefers 3-month ring |
| Fewer clinic or pharmacy visits | ''I would like a longer period due to the fact I don't like to go to the doctor a lot. And that's, that's you know, that's a lot of people's problems, the doctor's appointments.'' 1-month ring, Birmingham, Rating: 5, No duration preference |
| | ''I would, I would do thirteen [week ring] because just…You don't have to think about it, you don't have to deal with it, you don't have to, oh, a lot of those things, I know with the NuvaRing I had to go to the pharmacy every like month because they'd give me one at a time, and like that's super annoying.'' 3-month ring, San Francisco, Rating: 6, Prefers 3-month ring |

Table 4. Illustrative Quotes on Concerns About a 3-Month Ring

| *Theme* | *Illustrative quotes* |
|---|---|
| A. Hygiene and safety | |
| Concerns | ''Part of it was I wished I'd gotten a longer one so I didn't have to change them out, I guess more convenient, but I liked that I was changing it simply because it seemed like it would be safer, so like there would be fewer side effects if the same one wasn't in quite as long.'' 1-month ring, Birmingham, Rating: 5, Prefers 3-month ring |
| Alleviation over time | ''I was kind of concerned to leave something in that long, I was kind of worried about like would it cause like a bacteria infection or could I possibly take it out and rinse it off and put it back in. [laughter] Just to like clean it. So that was a concern. But everything was fine.'' 3-month ring, Birmingham. Rating: 8, Prefers 1-month ring |
| Influence on ring preference | ''Okay… I think the one month one would probably be better for me because leaving something in for three months, even though it's probably not unhygienic it feels like there's, something in there that long just doesn't seem right [laughter] And with it being a monthly thing, you know, taking it out right after your menstrual cycle and putting a new one in, you're, it's going to be a lot easier to remember because you're, you know, you're going to have that every month so it'll be easy to keep track of.'' 1-month ring, San Francisco, Rating: 8, No duration preference |
| B. Perceived side effects | |
| Little influence on acceptability | ''You know, like when you're wiping, I mean, it's just like, I was like, 'Wow, that's a lot.' It [the discharge] took me by surprise but afterward, after a couple times I was just used to it, I just knew that I had to have extra tissue, you know, to wipe. [laughter] And like I said, as long as it wasn't to where I'm walking around during the day and I need a pad, I didn't care.'' 3-month ring, Birmingham, Rating: 10, Prefers 3-month ring |
| Considered a drawback | ''I: … what do you think of as some drawbacks of using it for three months straight?<br>R: Well, like, like the discharge, having it for three months straight, or frequent bacteria infections, frequent yeast infections, like just ongoing complications. For a whole three months.<br>I: Sure. Do you think those are more likely to occur with a three month ring rather than a one month ring?<br>R: Yes…Because the ring is inside constantly, inside your body constantly for three months versus a month it gets to come out, you know, and your body take a breather for a little while, however long, and then, you know, [laughter] it goes back in.'' 3-month ring, Birmingham, Rating: 6, Prefers 3-month ring |
| Influence on ring preference | ''I: Okay. And so given the options of like having a, a monthly ring versus a three month long ring, which one do you personally prefer?<br>R: I don't know, I mean, I would be kind of curious to try the, the one month one so that I could, maybe like my, my side effects [pain during sex, menstrual cramping, vaginal discharge] while using the 3-month ring might be different if I, if it wasn't like such a high concentrated amount…. I think for me it would, they would probably be the same, [laughter] depending on if the side effects were different or not, but.'' 3-month ring, San Francisco, Rating: 7, No duration preference |
| C. Experiences with menses | |
| Little influence on acceptability | ''R: Yes, I had a period every month while I was on the study.<br>I: Okay. And how, how was that, using the ring and also menstruating?<br>R: It was fine. It was like about the same as usual.'' 3-month ring, San Francisco, Rating 5, Prefers 3-month ring |
| Influence on ring preference | ''Personally, for me, every time I've come on, the three months I've had it, every time I've come on [started menstruating] I've had to make sure that it stayed in place… So it wasn't, I wouldn't say it was uncomfortable, it would get a little frustrating. But not to the point to where I wouldn't use it. I would use it if I had to.'' 3-month ring, Birmingham, Rating: 9, Prefers 1-month ring<br>''But it was, it was I guess my concern was the old blood building around the ring … It's just like how long is the blood sitting there or, you know, would it be possibly to take the ring out while you're on your cycle maybe and putting it back in so you don't have to worry about it… I mean, other than that it was like a really great ring, I mean… I didn't see any negative side effects personally... just like, just keeping it in three months was like the only drawback for me.'' 3-month ring, Birmingham, Rating 8, Prefers 1-month ring |

been able to remove the ring and clean it on a weekly basis. These concerns were not tied to quantitative acceptability ratings and were often described as occurring early in the study and diminishing as participants used the ring over time. However, the two IDI participants in the 1-month group who expressed no preference for ring duration attributed their indecision to the balance of hygiene versus convenience. They also echoed a perceived benefit from other 1-month ring users that replacement could be aligned with menstrual cycle, which they felt was more intuitive than a

quarterly schedule, and made it easier to create a ring replacement routine.

During IDIs, several 3-month ring users reported bothersome changes or side effects, including increased discharge, change in vaginal odor, yeast infections, bacterial vaginosis, and constipation, which were often attributed to ring use (Table 4, Theme B). The degree to which these impacted ring acceptability varied substantially. Two participants described increased discharge that did not bother them, and one rated the ring a 10 despite this change. In contrast, side effects—or the threat thereof—were considered significant drawbacks for other participants. For example, one associated increased discharge with a higher risk of vaginal infection despite not experiencing any infections, and another experienced multiple yeast infections that reduced her comfort with the ring and caused her to remove it multiple times. Another participant attributed her experiences with pain during sex, increased menstrual cramping, and a higher volume of vaginal discharge to use of the 3-month ring. Because she suspected—but was not certain—that the 1-month ring might have fewer side effects, and did not feel it would create an additional burden, she stated no preference for either ring duration.

Similar patterns emerged with participants' experiences wearing the ring during menses and not being able to change it afterward (Table 4, Theme C). Many IDI participants did not have regular menses due to their contraceptive method, and most who had their menses while wearing the ring were not bothered by it or expressed minimal discomfort. Among those who had menses, about half noted minor, unbothersome changes to menstrual flow (both heavier and lighter) or to menstrual management practices to accommodate protocol restrictions (*i.e.,* no use of menstrual cups and no tampon use in the 24 hours before each study visit). Two participants, however, had experiences that were unpleasant enough to influence ring preference: One participant described challenges keeping the ring in place during menstruation, which worried and frustrated her. Though she expressed high satisfaction with the 3-month ring, she would prefer a 1-month ring to address these challenges. Another participant reported preferring a 1-month ring due to concerns about sanitation while wearing the ring during menses, despite having an otherwise positive experience.

Other concerns, less often cited, related to the larger dose of DPV in the 3-month rings, which might cause more side effects, and concerns that the 3-month ring would become less efficacious over time and decrease protection during the end of their 3-month use period. Some participants also expressed concerns about forgetting to replace a ring that was kept in for 3 months at a time. As one participant described this potential drawback: ''Forgetting about it so that it's, you know, six months later and you go, 'Oh, crap, I didn't take care of that''' (3-month ring, San Francisco). Finally, many saw pros and cons to both durations and felt that it was a matter of preference, which should be up to the individual user:

> ''I think it should be like an option. If the ring goes on the market they should have like a one month ring and then a three month ring because everybody likes being able to have different options.'' (3-month ring,, Birmingham)

## Discussion

In this phase I trial, both 3-month and 1-month vaginal rings were highly acceptable by the end of the study, and they were found to be comfortable and easy to use. However, the 1-month ring had consistently higher ratings throughout the study. Although there were no safety concerns identified, and no differences in grade ≥2 genitourinary adverse events between arms,[14] participants using the 3-month ring reported more changes to the vaginal environment, and they expressed concerns about the hygiene and safety of a ring left in place for so long.

To our knowledge, this is the first study of a vaginal ring worn continuously for 3 months for HIV prevention, but similar concerns about hygiene and side effects have influenced acceptability in studies of other rings. In a randomized trial of contraceptive rings with varying cycle durations, 1-month cycles had higher acceptability than 2-month, 3-month, or 12-month cycles primarily due to lower rates of unscheduled bleeding.[17] In a study of a placebo ring worn for 3 months that was removed monthly, rinsed, and re-inserted, menses and cleaning were among the most commonly reported reasons for off-schedule voluntary removal of the ring,[18] and similar concerns were reported in focus group discussions about hypothetical longer acting rings.[11,12,19] Participants also expressed concerns about hygiene and use during menses in previous studies of the 1-month DPV ring,[20,21] and both discomfort wearing the ring during menses and problematic changes to the vaginal environment predicted nonadherence to the ring in one phase 3 trial.[22]

As previously reported, our participants' concerns were mitigated as they became more familiar with the products, and the acceptability of both ring durations increased over time.[18,21,23–25] However, ratings did not increase until study exit (after 91 days) among participants using the 3-month rings, whereas in the 1-month arm they increased after 1 month of use and remained high thereafter. This suggests that participants withheld judgment until they had completed a full cycle of ring use, and that additional support may be required throughout this initial period if a 3-month ring becomes available for future use. Counseling, peer support, and educational videos may all be effective methods of addressing concerns and overcoming initial barriers to use.[26–28] Hygiene concerns might also be alleviated by allowing women to briefly remove the ring for rinsing (*e.g.,* after menses), as is already recommended in case of ring expulsion and before reinsertion. Future studies should explore whether this practice would impact product effectiveness.

Although the 1-month ring had higher acceptability ratings, a substantial majority of participants stated that they would prefer to use a longer duration (3-month) ring at study exit. Some previous studies have found strong participant preferences for long-acting HIV prevention products, whereas others concluded that preferences vary by individual or that other factors such as efficacy and delivery form outweigh duration of use.[12,29–34] Our qualitative findings suggest that in this context, stated preference was driven by the greater convenience of a 3-month ring, which would require fewer trips to the clinic, fewer insertions and removals, and less mental burden of having to think or worry about replacing the ring. Skepticism about the hygiene and safety of the 3-month ring was common and may have reduced acceptability for some participants; this interpretation is reinforced by the fact that preference for the 3-month ring was highest in the subgroup of participants who did not wear it during menses and did not encounter the hygiene concerns associated with leaving it in

after menses. However, the primary reason for not wearing the ring during menses was not experiencing menses during the study, and ring removals due to menses were rare. For most participants, the convenience of the 3-month ring outweighed their concerns, and this was true for participants assigned to the 1-month ring during the study as well as those assigned to the 3-month rings.

There were notable exceptions to the dominance of the 3-month ring preference within some demographic subgroups and among a few IDI participants. Stated preference for a 3-month ring was lower among participants who were from the Birmingham site, were African American, or did not have a college education; however, reasons for these group differences are unclear. Among IDI participants, those who did not prefer a 3-month ring described distinctive experiences or attitudes related to menses, hygiene, and side effects that were not reported by others in the sample. Future research should explore reasons for differing levels of comfort with an extended duration ring; some possibilities could include menstrual or vaginal hygiene practices, health care access and utilization, and the potential role of medical mistrust and health care discrimination in preferring the more thoroughly tested 1-month ring over the novel 3-month rings tested in this study.[35–39]

The mixed-methods design of this study provided a rich understanding of factors influencing acceptability and preference. Quantitative findings identified overall differences in acceptability that were not apparent in IDIs, highlighted the bothersome changes to the vaginal environment experienced by participants in the 3-month arms, and suggested that discomfort wearing the ring during menses was a strong predictor of preference. Differences in hygiene and safety worries were not detectable in the quantitative data, perhaps due to the small sample size or because participants did not feel that their discomfort or uncertainty was severe enough to report as a ''worry.'' However, this discomfort emerged as a central theme in the qualitative data, along with the central role of convenience, providing greater insight into participants' beliefs and experiences.

Several limitations should be noted. First, the study did not employ a crossover design, so participants could not directly compare the 1- and 3-month rings. This consideration may help explain the apparent discrepancy between acceptability and preference, as participants based their stated preference on their experience with their assigned ring duration, and may have made different assumptions about how their experience would differ with the other duration, and the relative acceptability of the two. The findings suggest that all else being equal, participants would prefer a longer duration ring, but that their choice between two specific rings might ultimately depend on other characteristics such as side effects or whether it could be removed and cleaned after menses. Second, because the sample size was small, we had limited power to detect differences between groups, and randomization did not result in a complete balance of baseline characteristics by arm. In particular, participants assigned to the 1-month ring were more likely to have prior vaginal ring use experience and higher acceptability ratings for a vaginal ring at baseline (irrespective of duration), which may have influenced subsequent perceptions of acceptability. However, the observed differences in acceptability during follow-up persisted when controlling for baseline ratings, suggesting that baseline differences did not fully account for the findings. Third, acceptability and preference are nuanced concepts that are difficult to measure; our quantitative questions may have missed key components of some women's experiences or unintentionally biased responses. Fourth, the qualitative sample was not intended to assess differences by site or demographic characteristics, and no insights could be gained on demographic variations in ring preferences. Finally, this phase 1 study focused on safety and pharmacokinetics and did not recruit participants based on HIV risk levels, so the findings may not be generalizable to higher risk women who would be more likely to use the ring in the future. However, for the 1-month ring, acceptability findings from phase 1 and 2 studies with lower risk women[18,24,40] largely predicted those from larger studies among higher risk women,[20,22,41] and participants in the current study reported that they would be highly likely to use the ring if it were found effective.[14]

## Conclusions

The 3-month DPV vaginal ring was highly acceptable after the first cycle of use, and the majority of participants stated a preference for a 3-month duration ring over a 1-month ring, primarily due to its convenience. However, many reported underlying concerns with an extended duration ring, including hygiene, use during menses, and side effects. If the 3-month ring reduces HIV risk and is approved for use in the future, women who select it may need additional support during the first cycle of use to overcome these concerns. In addition, there are some women for whom concerns about a longer duration ring outweigh its greater convenience, and who will continue to prefer a 1-month ring. Providing a range of duration options may help increase uptake of the ring as an HIV prevention method and expand its public health impact.

## Acknowledgments

The authors are grateful to the study participants for their participation and dedication. They thank the study team members at the research sites, at the MTN-036 Protocol Management team, and at the MTN Leadership Operations Center for their contributions to data collection.

## Authors' Contributions

S.T.R., I.H., E.L., B.M., T.W., C.H., T.M., C.P.D.I., J.M.P., A.L., and A.V.S. assisted with protocol development and design of this analysis. I.H., T.W., C.H., and A.L. collected data for the study. S.T.R., I.H., and E.L. conducted the analyses and wrote the article. All authors reviewed, edited, and approved the final article.

## Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

## Author Disclosure Statement

A.L. and A.V.S. have led studies in which Gilead Sciences has donated study drug. A.L. has received funding from Gilead and Viiv Healthcare for investigator-sponsored research. The other authors have no competing financial interests.

## Funding Information

The study was designed and implemented by the MTN funded by the National Institute of Allergy and Infectious Diseases through individual grants (UM1AI068633, UM1AI068615, and 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 (NIH). The IPM developed the 3-month and 1-month DPV rings, and it was the IND sponsor and supplied rings for this study.


## Supplementary Material

Supplementary Table S1
Supplementary Table S2

## References


1. UNAIDS data 2020. Geneva, Switzerland: UNAIDS, 2020.
2. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med 2016;375:2121–2132.
3. Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. N Engl J Med 2016;375:2133–2143.
4. Baeten JM, Palanee-Phillips T, Mgodi NM, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): An open-label, extension study. Lancet HIV 2021;8:e87–e95.
5. Nel A, van Niekerk N, Van Baelen B, et al. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): An open-label, extension study. Lancet HIV 2021;8:e77–e86.
6. European Medicines Agency. Dapivirine vaginal ring 25Mg H-W-2168: Summary of product characteristics. Amsterdam, The Netherlands: European Medicines Agency, 2020.
7. Brown E, Hendrix C, van der Straten A, et al. Greater dapivirine release from the dapivirine vaginal ring is correlated with lower risk of HIV-1 acquisition: A secondary analysis from a randomized, placebo-controlled trial. J Int AIDS Soc 2020;23:e25634.
8. Trussell J. Contraceptive failure in the United States. Contraception 2011;83:397–404.
9. Diedrich JT, Zhao Q, Madden T, Secura GM, Peipert JF. Three-year continuation of reversible contraception. Am J Obstet Gynecol 2015;213:662.e1–e662.e8.
10. Hubacher D, Spector H, Monteith C, Chen PL, Hart C. Long-acting reversible contraceptive acceptability and unintended pregnancy among women presenting for short-acting methods: A randomized patient preference trial. Am J Obstet Gynecol 2017;216:101–109.
11. Rosen RK, Van Den Berg JJ, Vargas SE, et al. Meaning-making matters in product design: User's sensory perceptions and experience evaluations of long-acting vaginal gels and intravaginal rings. Contraception 2015;92:592–601.
12. Weinrib R, Browne EN, Shapley-Quinn MK, et al. Perspectives from young South African and Zimbabwean women on attributes of four (placebo) vaginal microbicide delivery forms. AIDS Behav 2020;24:637–647.
13. Woodsong C, Holt JDS. Acceptability and preferences for vaginal dosage forms intended for prevention of HIV or HIV and pregnancy. Adv Drug Deliv Rev 2015;92:146–154.
14. Liu AY, Dominguez Islas C, Gundacker H, et al. Phase 1 pharmacokinetics and safety study of extended duration dapivirine vaginal rings. J Int AIDS Soc 2021;24:e25747.
15. Mensch BS, Katzen LL, Van der Straten A. Acceptability in microbicide and PrEP trials: Current status and a reconceptualization. Curr Opin HIV AIDS 2014;7:534–541.
16. O'Connor C, Joffe H. Intercoder reliability in qualitative research: Debates and practical guidelines. Int J Qual Methods 2020;19:1–13.
17. Miller L, Verhoeven CHJ, in't Hout J. Extended regimens of the contraceptive vaginal ring: A randomized trial. Obstet Gynecol 2005;106:473–482.
18. van der Straten A, Montgomery ET, Cheng H, et al. High acceptability of a vaginal ring intended as a microbicide delivery method for HIV prevention in African women. AIDS Behav 2012;16:1775–1786.
19. Guthrie KM, Vargas S, Shaw JG, et al. The promise of intravaginal rings for prevention: User perceptions of biomechanical properties and implications for prevention product development. PLoS One 2015;10:1–17.
20. Duby Z, Katz AWK, Browne EN, et al. Hygiene, blood flow, and vaginal overload: Why women removed an HIV prevention vaginal ring during menstruation in Malawi, South Africa, Uganda and Zimbabwe. AIDS Behav 2020;24:617–628.
21. Van Der Straten A, Panther L, Laborde N, et al. Adherence and acceptability of a multidrug vaginal ring for HIV prevention in a phase I study in the United States. AIDS Behav 2016;20:2644–2653.
22. Browne EN, Mayo AJ, Montgomery E et al. Acceptability of and adherence to the dapivirine vaginal ring for HIV-1 prevention. In: 4th International Conference on HIV Treatment and Prevention Adherence, Miami Beach, FL, 2019.
23. Griffin JB, Ridgeway K, Montgomery E, et al. Vaginal ring acceptability and related preferences among women in low-And middle-income countries: A systematic review and narrative synthesis. PLoS One 2019;14:1–22.
24. Montgomery ET, Van Der Straten A, Cheng H, et al. Vaginal ring adherence in sub-saharan Africa: Expulsion, removal, and perfect use. AIDS Behav 2012;16:1787–1798.
25. Bauermeister JA, Golinkoff JM, Carballo-Diéguez A, et al. A mixed-methods study examining adherence to and acceptability of intravaginal rings for HIV prevention: Behavioral results of MTN-027. AIDS Behav 2020;24:607–616.
26. van der Straten A, Browne EN, Shapley-Quinn MK, et al. First impressions matter: How initial worries influence adherence to the dapivirine vaginal ring. J Acquir Immune Defic Syndr 2019;81:304–310.
27. Weinrib R, Minnis A, Agot K, et al. End-users' product preference across three multipurpose prevention technology delivery forms: Baseline results from young women in Kenya and South Africa. AIDS Behav 2018;22:133–145.
28. Katz AWK, Naidoo K, Reddy K, 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;24:2387–2399.
29. Shapley-Quinn MK, Manenzhe KN, Agot K, Minnis AM, van der Straten A. ''We are not the same'': African women's view of multipurpose prevention products in the TRIO clinical study. Int J Womens Health 2019;11:97–107.
30. Minnis AM, Browne EN, Boeri M, 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;80:394–403.
31. Montgomery ET, Atujuna M, Krogstad E, et al. The invisible product: Preferences for sustained-release, long-acting pre-exposure prophylaxis to HIV among South African youth 2019;80:542–550.
32. Minnis AM, Atujuna M, Browne EN, et al. Preferences for long-acting pre-exposure prophylaxis (PrEP) for HIV prevention among South African youth: Results of a discrete choice experiment. J Int AIDS Soc 2020;23:1–10.
33. Browne EN, Montgomery ET, Mansfield C, et al. Efficacy is not everything: Eliciting women's preferences for a vaginal HIV prevention product using a discrete-choice experiment. AIDS Behav 2020;24:1443–1451.
34. Quaife M, Eakle R, Cabrera Escobar MA, et al. Divergent preferences for HIV prevention: A discrete choice experiment for multipurpose HIV prevention products in South Africa. Med Decis Mak 2018;38:120–133.
35. Tekeste M, Hull S, Dovidio JF, et al. Differences in medical mistrust between black and white women: Implications for patient–provider communication about PrEP. AIDS Behav 2019;23:1737–1748.
36. Ball K, Lawson W, Alim T. Medical mistrust, conspiracy beliefs & HIV-related behavior among African Americans. J Psychol Behav Sci 2013;1. DOI: 10.15640/jpbs.
37. Smirnoff M, Wilets I, Ragin DF, et al. A paradigm for understanding trust and mistrust in medical research: The Community VOICES study. AJOB Empir Bioeth 2018;9: 39–47.
38. Institute of Medicine (US) Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. In: Smedley BD, Stith AY, Nelson AR, eds. Unequal treatment: Confronting racial and ethnic disparities in health care. Washington (DC): National Acadamies Press, 2003. DOI: 10.17226/12875.
39. Dovidio JF, Penner LA, Albrecht TL, Norton WE, Gaertner SL, Shelton JN. Disparities and distrust: The implications of psychological processes for understanding racial disparities in health and health care. Soc Sci Med 2008;67:478–486.
40. Nel A, Bekker L-G, Bukusi E, et al. Safety, acceptability and adherence of dapivirine vaginal ring in a microbicide clinical trial conducted in multiple countries in Sub-Saharan Africa. PLoS One 2016;11:e0147743.
41. Montgomery ET, Van Der Straten A, Chitukuta M, et al. Acceptability and use of a dapivirine vaginal ring in a phase III trial. AIDS 2017;31:1159–1167.

Address correspondence to:
*Sarah T. Roberts, PhD*
*Women's Global Health Imperative (WGHI)*
*RTI International*
*2150 Shattuck Avenue, Suite 800*
*Berkeley, CA 94704*
*USA*

*E-mail:* sroberts@rti.org