Favoring “Peace of Mind”: A Qualitative Study of African Women’s HIV Prevention Product Formulation Preferences from the MTN-020/ASPIRE Trial

Ariane van der Straten, PhD,^{1,2} Mary Kate Shapley-Quinn, MPH,¹ Krishnaveni Reddy, MB BCh,³
Helen Cheng, MS,¹ Juliane Etima, MA,⁴ Kubashni Woeber, MBA, MMed Sc,⁵ Petina Musara, BSc,⁶
Thesla Palanee-Phillips, MMed Sci, PhD,³ Jared M. Baeten, MD, PhD,⁷
and Elizabeth T. Montgomery, PhD,¹ on behalf of the MTN-020/ASPIRE Study Team

Abstract

Several formulations of HIV pre-exposure prophylaxis (PrEP) have shown varying levels of effectiveness in women. Little information is known about preference across formulations, especially among product experienced women. Seventy-one women (48% married; median age 26; range 18–45) who were participating in a vaginal ring trial for HIV prevention in Malawi, South Africa, Uganda, and Zimbabwe underwent an in-depth interview at their last study visit, during which they were presented with pictures and descriptions of nine possible product formulations (male and female condoms, oral tablets, injectables, implants, and a vaginal gel, ring, insert, and film). Each formulation was discussed, highlighting salient attribute(s) and contextual factors that may have informed stated preferences. Participants expressed most interest for long-acting PrEP formulations (rings, 94%; implants, 39%; injections, 34%), which were generally favored over short-acting ones. Participants appreciated the continuous protection offered, discreet usage, and the advantage of “peace of mind” imparted by simplified use and infrequent dosing, alleviating worries around forgetting doses. Preferred attributes of short-acting formulations included reversibility, user control, ease of administration, and low toxicity. Participants were least interested in the oral tablets (due to the daily dosing, difficulty swallowing pills, and HIV-related stigma), and the vaginal gel and film (due to vaginal insertion, coital dosing, effect on sex, and unfamiliarity with the method). Dislike for vaginally administered products was more pronounced among young women. Multiple factors played into potential users’ considerations for preferred formulations, emphasizing how a suite of options for prevention might best respond to women’s needs and wants.

Keywords: microbicide, vaginal ring, PrEP, biomedical HIV prevention, women, Africa, formulation(s), qualitative study

Introduction

IN THE PAST decade, significant progress has been made in expanding the toolbox of HIV-1 prevention options for women and girls, who account for ~60% of people living with HIV in sub-Saharan Africa.¹ Different pre-exposure

prophylaxis (PrEP) approaches have shown varying levels of effectiveness² in preventing male to female sexual transmission of HIV, including the vaginal microbicide 1% tenofovir gel used pericoitally,³ oral daily dosing of tenofovir-emtricitabine tablets (TruvadaTM, approved for PrEP among women and other vulnerable populations),^{4,5}

¹Women’s Global Health Imperative (WGHI), RTI International, San Francisco, California.

²Department of Prevention Medicine, Center for AIDS Prevention Studies (CAPS), University of California San Francisco, California.

³Wits Reproductive Health and HIV Institute (Wits RHI), Johannesburg, South Africa.

⁴Makerere University—Johns Hopkins University Research Collaboration, Kampala, Uganda.

⁵Medical Research Council, Durban, South Africa.

⁶UZ-UCSF Collaborative Research Programme, Harare, Zimbabwe.

⁷Department of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, Washington.

and most recently, the monthly dapivirine vaginal ring.^{6,7} Other promising delivery forms of antiretroviral-based prevention are at the preclinical or clinical stage, including tenofovir-based rings,^{8,9} injectables,¹⁰ vaginal films, vaginal inserts (or suppositories),¹¹ and implants.^{12,13}

Despite these landmark successes, optimal use of these prevention technologies has been an ongoing challenge. Indeed, several prevention trials failed to demonstrate effectiveness, attributed in large part to low adherence to daily or pericoital use regimens.^{14–16} Similarly, the monthly vaginal ring conferred less protection to women with evidence of lower ring adherence, including younger women.⁶

End-user input on preferred product attributes has been recognized as a key determinant informing product development and rollout, as acceptability constitutes an important driver of uptake and adherence.^{17,18} Studies of hypothetical surrogates and actual HIV prevention and contraceptive products have shown common product attributes that weigh into women's decisions about what they prefer or are willing to use. These include effect on sex,^{19–21} discreetness,^{22–24} user burden,^{11,25,26} familiarity,^{26,27} efficacy,^{20,28–30} side effects,^{23,31} as well as the duration and timing of dosing.^{26,32,33} Other attributes are relevant for some products only, such as effect on menses (for formulations with a hormonal contraceptive^{19,31}) or volume and consistency for dissolvable vaginal products such as gels and films.^{32,34,35}

Given the growing number of HIV PrEP options becoming available and the promise of several more in the development pipeline, we conducted a multi-country qualitative evaluation of HIV PrEP formulation preferences among women participating in ASPIRE/MTN-020, an HIV prevention trial.⁶

Methods

ASPIRE study

The MTN-020/ASPIRE trial design, population, procedures, and primary findings have been previously published.^{6,36} Briefly, this was a randomized, placebo-controlled phase III trial conducted between August 2012 and June 2015, which evaluated the safety and effectiveness of a monthly dapivirine vaginal ring for HIV prevention in 2629 participants. HIV-seronegative women aged 18–45 from 15 sites in four countries (Malawi, South Africa, Uganda, and Zimbabwe) were randomized (1:1 ratio) to receive a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine or a placebo ring and followed up for a duration of 12–33 months. At each monthly visit, participants were provided with (a) a new ring and instructions to use it for 28 days continuously as part of ring adherence counseling and (b) male condoms and instructions to use one for each act of vaginal or anal sex as part of HIV risk reduction counseling. Participants were provided with (and required to use) modern contraceptives, monthly HIV and pregnancy tests, as well as quarterly sexually transmitted infections (STI) diagnostic tests and treatment, as needed.⁶ Women were not eligible to enroll if they had participated in a microbicide or PrEP trial in the past 12 months.

The ASPIRE qualitative component procedures were conducted from February 2013 to June 2015 at six study sites, covering the four trial countries. Qualitative participants were randomly recruited into one or more in-depth interviews (IDIs) or focus group discussion. In addition, special cases (e.g., seroconverters, those reporting positive or negative issues with

partner and/or adherence) were purposively recruited to undergo an IDI. Interviews followed semistructured guides administered by trained social scientists in local languages and were audio-recorded, transcribed verbatim, and translated into English. Further detail on the qualitative methodology and the main qualitative findings have been presented elsewhere.³⁷

This analysis includes data on product preferences collected at the qualitative participants' final clinic visit ($N=71$) that occurred at, or immediately after, their last use of the study ring. At that visit, the participant received an IDI, during which they were presented with a showcard of nine possible PrEP formulations, including the vaginal ring and male condoms provided to them during the ASPIRE study (Fig. 1). Participants were asked "How does the ring compare with other products that are currently used to prevent HIV or may be used in the future?" Brief descriptions were read by the interviewer for each formulation, including a statement that oral tablets and male and female condoms were already proven to protect against HIV (Fig. 1). For investigational formulations (vaginal ring, vaginal gel, vaginal films, vaginal inserts, injectables, or implants), interviewers described the most recent dosing used either in HIV prevention studies or for the contraceptive indication. Women were also asked to select what formulation(s), if any, they most and least preferred and to explain their selections. Women could select as many products as they wanted in each group, but could not select the same product for both most and least preferred.

The ASPIRE study protocol, including its qualitative component, was approved by the Institutional Review Boards at each of the corresponding study sites, and was overseen by the regulatory infrastructure of the US National Institute of Health and the Microbicide Trials Network (MTN).

Data analysis

Descriptive statistics were used to present demographic and background data, as well as frequencies of "most" and "least" preferred product formulations (SAS version 9.4 Cary, NC). We also examined bivariate associations between age group (women aged 18–24 years old vs. ≥ 25 years old) and product formulation preference using Fisher's exact test.

The interview guides, codebook, and the analysis strategy were framed around a conceptual framework focused on PrEP, and microbicide acceptability and adherence. This framework examines product acceptability as a unique construct, distinct from adherence; considers the effect of broader contextual factors on both acceptability and/or adherence; and posits preference and choice as intermediary constructs related both to acceptability and adherence.¹⁸

Textual data from transcripts were coded (average inter-coder reliability $\geq 80\%$) and qualitatively analyzed using NVivo11 software as previously described.³⁷ The qualitative analyses presented in this study are based on the code "product preference." Summaries of textual excerpts for this code were stratified by age (<25 and ≥ 25 years old) and analyzed for salient themes related to hypothetical acceptability, attributes of formulations, and contextual factors informing stated product preferences.

Results

Seventy-one ASPIRE qualitative participants were included in this analysis of stated preference for nine HIV PrEP

Product Formulations for HIV Prevention: Existing and Under Development

FIG. 1. Showcard of nine potential product formulations for HIV prevention

Key Attributes of Product Formulations:

Vaginal Gel: vaginally administered using an applicator, inserted daily or pericoitally; **Oral Tablets:** orally administered, used daily, already proven to protect against HIV; **Injectables:** injected using a needle, administered once every two-three months; **Vaginal Film:** vaginally administered using fingers, inserted daily or pericoitally; **Vaginal Ring:** vaginally administered using fingers, replaced once a month or less frequently (once every three months); **Male & Female Condoms:** male condoms applied using finger, female condoms vaginally inserted using fingers, both used coitally, already proven to protect against HIV; **Vaginal Suppository/inserts:** vaginally administered using finger or an applicator, inserted daily or pericoitally; **Implants:** flexible plastic rods placed under the skin of the upper arm; for contraception, implants are inserted every 3-5 years.

formulations. Table 1 describes the participants' country, age, sexual behavior, contraceptive method, duration of follow-up, and seroconversion status.

Of the nine formulation options described and presented on the show card, women selected a median of 2 (range 1–8) as most preferred and a median of 2 (range 0–8) as least preferred formulations. The vaginal ring was selected as most preferred by 94% of participants, followed in descending order by implants (39%), injectables (33%), male condoms (27%), and oral tablets (11%). Fewer than 10% selected each of the remaining formulations (female condoms, vaginal insert, film, or gel) as a most preferred formulation (Fig. 2a). Reciprocally, oral tablets were most commonly selected as least preferred formulation (61%) followed by vaginal gel (55%) and vaginal film (41%). Over a quarter to a third of participants selected vaginal inserts, male and female condoms, injections, and implants as least preferred formulations. One participant selected the ring as the least preferred formulation. Although this participant did not specifically mention attributes of the ring she disliked, she experienced an array of issues during the trial, including conflicts with her male partner, illness that caused her to decide to remove the ring, and eventual HIV seroconversion. The six other women who HIV seroconverted selected the vaginal ring as a preferred formulation, and none of their comments or opinions differed in any striking way from the rest of the sample.

In bivariate analyses, age group was associated with preference ranking, with those aged 18–24 less likely to select male condoms ($p < 0.05$) or vaginal inserts ($p < 0.07$) as most preferred, and more likely to select these products as

well as vaginal films ($p < 0.01$) as least preferred formulations (Fig. 2b, c).

Long-acting versus short-acting formulations

An overall preference for long-acting formulations (the vaginal ring, implants, and injections) emerged from both the ranking exercise and IDI discussions. Reciprocally, there was less interest for short-acting formulations that required daily or coital dosing. Nevertheless, women highlighted pros and cons to both types of products, and when short-acting formulations were preferred, it was often because participants were familiar with a given product, prioritized protection from other STIs (e.g., with condoms), thought the administration process was simple, and liked that they were easily reversible and female/user initiated (Table 2). Long-acting formulations were seen favorably, as being discreet, highly effective, and imposing a low burden on the user. Furthermore, female initiation and full reversibility were important features of the vaginal ring that other long-acting formulations did not have. This was highlighted by this participant who valued the ring as a method that would not mark or alter her body:

Another thing I can say I like about the ring is that it gives me **peace of mind**. Because for the time I have used it, it stays in one place and there is no way it has affected my body. Yet when you put a [finger] ring on a finger, you see that it puts a mark where it is placed. But I have not had any effect from the study ring. I like it because it has left me as I was before I started using it. (Uganda, age 26)

TABLE 1. CHARACTERISTICS OF THE SAMPLE

<i>Sample</i>	<i>Total (N=71)</i>
Baseline	
Country, % (n)	
South Africa	48 (34)
Uganda	18 (13)
Malawi	17 (12)
Zimbabwe	17 (12)
Age (years): median (mean, minimum–maximum)	26 (26.8, 18–42)
Some secondary school or more, % (n)	79 (56)
Married, % (n)	48 (34)
Has a primary sex partner, % (n)	100 (71)
More than one sex partner in the past 3 months, % (n)	14 (10)
Earns her own income, % (n)	52 (37)
Live births: median (mean, minimum–maximum)	2 (1.9, 0–5)
Contraceptive use at baseline, % (n)	
Injectable	52 (37)
Implant	24 (17)
IUD	13 (9)
Oral contraceptives	9 (6)
Sterilization	3 (2)
Condom use at last vaginal sex act, % (n)	42 (30)
Participated previously in an HIV prevention trial, ^a % (n)	4 (3)
Follow-up	
Duration in study (months): (mean, minimum–maximum)	(26.7, 15–34.1)
Seroconverters, ^b % (n)	10 (7)
Qualitative interview modality, % (n)	
Last serial interview	66 (47)
Special case interview	34 (24)

^aThree participants had participated in previous trials: two in HPTN-067 (oral PrEP)⁴³ and one in MDP 301 (coital gel).⁴⁴

^bParticipants had seroconverted in ASPIRE before interview. IUD, intrauterine device.

Participants considered a range of attributes and factors when discussing the nine formulations, which are presented below and summarized in Table 2 (with exemplary quotes).

Protection and safety

When explaining the rationale for why a formulation was (or was not) seen as favorable, participants often cited beliefs about its efficacy, as well as any anticipated side effects, as elements that affected their preference. For several of the investigational products, women stated that they would be of interest to them, despite other shortcomings, as long as they provided full protection.

Male and female condoms as well as oral tablets were described by interviewers as proven effective against HIV. Nevertheless, concerns were expressed for the oral tablets because women worried they would forget to take them, which would result in decreased or no protection, as they reported happens with the use of oral contraceptives.

For male condoms, potential for breakage and forgetfulness were common concerns that tempered their perceived effectiveness. Despite this, women commonly

appreciated condoms' known ability to protect against HIV and other STIs.

For products in the development pipeline, beliefs about biological efficacy and safety came, in part, from perceptions about the mode of administration and delivery system, as well as from experiences with similar formulations for contraception or for other indications. For example, formulations administered systemically were described as providing high protection due to circulation of the drug in the entire body, with the caveat that this may also increase risk of toxicity, since drug may accumulate in the body or lead to drug-to-drug interactions.

Because forgetting to take a product was a salient concern, long-acting formulations offered more worry-free options for consistent and continuous protection from HIV. Referring to the implant, this participant said:

You know that I am living with something that is protecting me and you won't have to worry about having to say 'so today I forgot to take like the pill,' or that I have forgotten to insert the vaginal film. (Zimbabwe, age 24)

Long-acting formulations were also seen as protective under a variety of circumstances, including unplanned or nonconsensual sex.

As for the condoms and vaginal film, these are not reliable in case one is raped because they do not offer full protection every time, unlike the ring. (Malawi, age 30)

On the other hand, women expressed concerns that long-acting systemic formulations would result in more exposure to drug and undesirable side effects like decreased fertility, weight gain, or making the vagina "watery." Often the type of side effects discussed came from those known for or told about contraceptives:

Most people who have inserted implants are getting fat. So I don't know if it [increases] appetite or what. I don't want to be fat, yhoo! (South Africa, age 22)

Product reversibility came up in discussions of safety and side effects. The potential for incompatibility between the drug and the body was seen as a major drawback of injections or implants, but it was also cited for oral tablets:

You may use the pills and they may not be compatible with you and yet the drug will be inside you already and cannot be taken out immediately compared to the ring... I now know that it [ring] has no side effects on me." (Zimbabwe, age 28)

Product attributes: dosing regimen and route of administration

The dosing regimen—whether a product was to be used coitally, daily, monthly, annually, and so on—received a lot of consideration; more frequent dosing was typically disliked because of the burden on the user:

It [vaginal film] makes one busy by inserting and re inserting while with the ring you just need to insert it once every month. (Malawi, age 21)

Thus, preference for long-acting formulations was also explained by an appreciation for infrequent dosing, fewer clinic visits and less opportunities to forget doses, the ease of administering the product at the clinic, and in the case of the implant and injection, nonvaginal administration.

FIG. 2. Most and least favored formulations: (a) overall, (b) most preferred by age group, and (c) least preferred by age group ($N=71$). Bivariate difference by age group; Fisher's exact test: $^{\dagger}p < 0.1$; $*p < 0.05$, $**p < 0.01$.

Nevertheless, concerns with injections or implants were commonly voiced, because of needle phobia, the pain or discomfort associated with the administration process, the reliance on skilled clinicians, and the invasive procedure.

I won't use it [implant]... I don't like something to be inserted under my skin... They said sometimes it shifts from where it was placed initially and you have to go back to clinic for the nurses to check it. (South Africa, age 42)

In that respect, some participants expressed concerns about clinical staff being unqualified to administer products (e.g., injection and implant) or performing invasive procedures. In

contrast, short-acting formulations were seen favorably for the opposite reasons: easy to insert or apply, removable after use (e.g., condoms), and user controlled.

Aside from the ring, women expressed concerns for products administered vaginally. They also stated that daily or coital products were tedious: putting on a condom or inserting a product vaginally before sex would be forgotten, burdensome, or plainly unpleasant. This dislike for products inserted vaginally was more apparent in the young age group:

I'm scared of anything that goes inside me [vagina] like this paper [the film]. (South Africa, age 18)

TABLE 2. ATTRIBUTES SEEN AS FAVORABLE AND UNFAVORABLE OF SHORT-ACTING (A) AND LONG-ACTING (B) FORMULATIONS, AND ASSOCIATED EXEMPLARY QUOTES

		<i>Pros and cons of short-acting formulations</i>	<i>Exemplary quotes</i>
A. Short-acting formulations			
1. Protection and safety	+	Known efficacy STI protection Systemic protection	Condom is a sure thing to protect against HIV. (South Africa, age 30)
	–	Unreliable (forgettable, not sturdy)	I do not like these oral tablets because even those for family planning we forget to take them and end up being pregnant. (Zimbabwe, age 31)
2. Product attributes	+	Female initiated Simple to insert/apply Removable	It [male condom] is something you take when you want to use it... After you have used it you remove it. (Zimbabwe, age 28)
	–	Tedious Vaginal administration Size, texture, feel	I won't be able [to use the vaginal gel]... Eish! Putting it inside you! ... It looks scary. (South Africa, age 18)
3. Attributes of use	+	Familiarity	I would insert them [vaginal inserts]... for me it's not a problem because I use tampons during menstruation, so I'm used to putting something inside me [inside her vaginal]. (South Africa, age 27)
	–	High user burden Supply or storage issues Inconvenient (e.g., travels) Scary; unknown	Because I do not understand, I wouldn't know on the issue that when it [vaginal insert] is inserted, will it dissolve or what becomes of it? (Zimbabwe, age 24)
4. Effects on sexual encounter	+	Does not interfere with sex	Because if they don't take [a long] time to dissolve, they are just the same as injections and oral tablets, that's why I say I can use them. If they take [a long] time to dissolve they could come out [during sex] without working. (South Africa, age 30)
	–	Requires planning Noticeable	With this [vaginal film] the sexual partner may come while you are not yet ready and he will just undress you and have sex. But with the ring, it is always there [in the vagina] so these are truly different. (Malawi, age 22)
5. Partner's attitude	–	Requires his approval Negative reactions	Because you should ask for the gel every time you have a sexual desire. I feel it cannot be good. A good method can be a ring because once inserted even your sexual partner cannot know that you have it. (Malawi, age 24)
		<i>Pros and cons of long-acting formulations</i>	<i>Exemplary quotes</i>
B. Long-acting formulations			
1. Protection and safety	+	High level of protection Worry-free product Feeling safe Reversibility	I don't like injections, I don't like needles... But then if it is something that is 99% proven that it prevents HIV probably it would be something that I will use. (South Africa, age 21)
	–	Systemic toxicity Drug–drug interactions side effects	I am afraid ...I don't know how it is going to be like in my body [the injection], I don't know if it is going to affect my health. (South Africa, age 23)
2. Product attributes	+	Infrequent administration Nonvaginal Simple to insert/apply	Where it [the implant] is put on the arm is different from these other methods which have to be injected or have to be inserted [down] there. Some find it hard to insert [into the vagina] but this one is "easy" it is put on the arm "plus" it stays longer. (Zimbabwe, age 23)
	–	Invasive Pain/discomfort with administration	I am afraid of the implant, I do not like it. I used to see people who insert it, my sister, their arms are blue as if a person has been beaten [them]. (South Africa, age 27)
3. Attributes of use	+	Low burden/cannot forget Discreet/cannot be seen Familiarity	It [ring] doesn't give me a tough time, because once you have inserted it, you are done, unlike the pills, which you have to be taking daily, and sometimes you can forget. (Malawi, age 19)
	–	Palpable Scary; unknown	It's not that I do not trust it [the implant], it just scares me. I fear the fact that you can feel it on the outside of your skin. (South Africa, age 22)

(continued)

TABLE 2. (CONTINUED)

		<i>Pros and cons of long-acting formulations</i>	<i>Exemplary quotes</i>
4. Effects on sexual encounter	+	No precoital action required	The ring is better than a condom because when you are going to have sex the ring is already inside you, unlike the condom that you have to wear before every sex act. (South Africa, age 30)
5. Partner's attitude	+	Not felt or seen by him	There is nothing visible to the partner for him to ask what you have put or anything [implant]. (Zimbabwe, age 23)
	–	Secret use possible	Sometimes you find your partner is fingering you and finds a ring, then that's followed by 21 questions. (South Africa, age 20)
		Palpable	
		Negative reactions	

Attributes of use: familiarity and discreteness

Overall, familiarity with a product was a major factor in influencing women's stated preferences. The female condom, vaginal film, gel, and insert elicited fearful reactions because women had not used, seen, or heard of them, or did not understand how they worked.

In contrast, use of the ring during the ASPIRE trial and widespread experience with male condoms, as well as contraceptive methods like injections and implants contributed to more favorable views.

The importance of discreteness was highlighted throughout women's explanations of preference as well—the palpability of the implant in the arm was a concern for some and the possibility that other people will see someone taking pills was disliked, whereas participants spoke highly of the invisibility of the injection and of the vaginal ring.

I would use the ring and the injectables. Though I don't like injectables but I would choose it because it cannot be seen, just like the ring. (South Africa, age 23)

The comfort of a given product was mentioned both in the context of administering the product (swallowing a tablet, receiving an injection, inserting an applicator of gel, inserting or removing the ring, and so on) and the product being used (e.g., wearing a ring for a month, using a condom during sex, and an implant remaining under the skin for years). A key favorable attribute of a formulation was the ability to forget it once taken, carry on one's daily life without interference, and its inconspicuousness to the user and those in her life. Finally, for short-acting formulations, the need to carry them when being away from home and the risk of discovery, as well as the anticipated issue of where to discreetly store these products in the house were of concern too.

Effects on sexual encounter

Noninterference and unobtrusiveness during sex was also paramount in preference rating. Overall, long-acting formulations were thought to have less impact on the sexual encounter because the user or her partner did not have to do anything before sex to apply the product and be protected, whereas the use of coitally dependent products, like condoms, can interrupt sex.

Although some participants thought vaginally applied products would not impact sex, more often they worried that products like condoms and vaginal gels, films, and inserts would require prior planning, a break in foreplay, and be

tactilely noticeable to their sex partner. In the case of the ring too, some women reported unexpected partner's discoveries, which resulted in scrutinizing and questioning. In that respect, systemic formulations (injection, implant, and oral tablet) were favored for their invisibility once taken, and therefore the ability to avoid unwanted questions from sex partners.

Partner's attitude

Aside from the male condom, all the formulations presented were female administered or used by women, which participants appreciated. However, as mentioned above, a paramount concern with several formulations was that a male partner could have a negative reaction if he discovered the use of one of these products, or was told about it. Women feared that if their partner could feel the vaginal ring, notice an implant under their skin, or the lubrication resulting from use of one of the other vaginal formulations, women would at minimum have to answer unwanted questions and at worse it could result in an altercation:

Can this not bring conflict in the family if your sexual partner has to see you applying [gel] each time? ...With the small houses, where do you go to apply it? Maybe those with bigger houses, they can go into a different room...but still one day your husband can discover it. (Malawi, age 24)

Thus, participants preferred products that they anticipated would be less noticeable to their partners.

Discussion

As the HIV epidemic continues to disproportionately impact young women in sub-Saharan Africa, studies have shown that options beyond the traditional abstinence, fidelity, and condoms are desired and needed.^{2,38,39} To that end, we explored stated preference for and interest in nine different potential HIV PrEP formulations, in a multi-country qualitative study nested within the ASPIRE/MTN-020 study. These included six female-initiated formulations (vaginal ring, gel, inserts, film, oral tablets, and female condoms), two provider-administered formulations (injections and implants), and male condoms. Overall, long-acting formulations were favored over short-acting ones for the continuous protection they would offer, discretion, together with “peace of mind” imparted by simplified use requirement and infrequent dosing. This, in turn, alleviated worries around forgetting to take the product or being unprotected if methods

are coitally dependant, in the case of unwanted sexual contact.^{40,41} Preferred attributes of short-acting formulations included reversibility, user control, ease of administration, and perceived low toxicity, another type of “peace of mind.” While no single product had all favored attributes, the vaginal ring was ascribed key features of both long-acting (e.g., infrequent dosing) and short-acting methods (e.g., full reversibility and user control). Furthermore, few participants associated the ring with side effects, and the ring had become familiar by virtue of its usage during the ASPIRE trial. Some drawbacks, however, derived from the vaginal administration, including the ring’s detectability during sex, and the insertion and removal process. This echoed findings from a larger analysis of ring acceptability in ASPIRE.^{37,42}

Aside from the vaginal ring, other vaginal products reportedly did not generate much interest, in part, because they were unknown, short acting, and perceived as inconvenient to use. Dislike for products vaginally administered was more pronounced among young women, which corroborates stated preference previously reported for the gel and other vaginal products.²⁶ In so far as preference may inform use, these findings could also contribute to explain lower adherence among young women in vaginal microbicide trials, including ASPIRE.^{6,14,15}

Lack of familiarity was a main reason for disregarding vaginal formulations other than the ring. It stemmed from the lack of familiarity both with this mode of administration and with the products themselves. Actually, familiarity proved favorable for PrEP formulations that resembled common contraceptive methods (e.g., injections and implants) and disfavored novel formulations including, inserts, films, and gels. Indeed, product novelty seemingly provoked uncertainty and suspicion rather than curiosity. Notably, although the male condom was both familiar and provided throughout the ASPIRE trial, a majority of women viewed it unfavorably, and more so among young women than among their older (age ≥ 25) counterparts. This suggests that familiarity, while important, may not be a determining attribute in generating or maintaining interest in a given formulation. Indeed, gender power imbalance and norms around condoms are well-known reasons why these are not liked (e.g., signals promiscuity, and relationship mistrust). Also, known or perceived side effects (e.g., pain of implant removal and weight gain with progestin injectables) negatively impacted women’s stated preference even if a method was familiar.

Injections were selected by about a third of participants as a most preferred formulation and by another third as the least preferred formulation. Similar (slightly more positive) rankings were given to implants. For both these methods that are provider administered, discussion of their attributes highlighted important points of considerations for future product development. On the positive side, anticipated efficacy was high, and infrequent dosing was liked with the expectation that these would be “worry-free” approaches, providing women with continuous coverage, in settings where timing of sex is dictated by men and concerns for nonconsensual sex are high.⁴¹ However the dislike of needles, the fear of pain, the invasive procedures, and the challenges with irreversibility linked to potential toxicity tempered participants’ interests in these systemic approaches. Interestingly, while reversibility for quick return to fertility is an important consideration for modern contraceptives,^{43,44} so far, it had not been highlighted

in the context of PrEP or microbicide. With the emergence of long-acting formulations, the same interest in a reversible method has surfaced, but here as a way to mitigate possible drug side effects and toxicity.

Another consideration with injectables or implants was misgivings about access to clinical settings and staff qualifications. For convenience, participants preferred methods that allowed for the least number of clinic visits possible. They also placed value on their impressions of the clinic staff’s competence. Some participants questioned the qualifications of clinic staff to do the more invasive procedures associated with long-acting methods, whereas others thought the clinic afforded a better environment for method administration because of issues with hygiene and increased opportunity for human error if methods are user administered.

Daily oral tablets were most frequently selected as the least preferred formulation. This is despite oral PrEP’s proven efficacy for HIV prevention. Notably, very few women in this sample had previously participated in oral PrEP or microbicide trials, given ASPIRE’s eligibility criteria.⁶ This contributed to low familiarity with oral PrEP. Nevertheless, all participants were familiar with medications taken orally, or with oral contraceptives. The major reason given for disliking daily tablets was fear of forgetting, and for this reason, they were classified as an unreliable approach, similar to condoms. As previously reported, some participants also viewed oral tablets as stigmatizing, likened to taking anti-retrovirals (ARV) when HIV positive or more generally with being sick.^{45,46} In this study, as in a previous qualitative study conducted following the VOICE trial, oral tablets and vaginal gels were among the least favored formulations because of their daily dosing requirement.²⁶

There are several limitations to this study. Since women were interviewed at the end of their participation in the ASPIRE trial; they are not representative of the general population in their countries and most likely had a positive bias toward the vaginal ring, and/or may have provided socially desirable responses to the interviewer. Still, using a sample with known experience with any HIV prevention product was seen as potentially advantageous in eliciting salient attributes of different PrEP formulations. Second, there was inconsistent knowledge of the nine formulations: participants had direct experience with ring and condoms, and not with others (e.g., film and gel). Interviewers also had different levels of familiarity with the nine formulations and due to the unstandardized nature of IDI, probed differently about these formulations. Recognizing this, our analysis focused on attributes and contextual issues influencing stated preferences, rather than on opinions on the products themselves. Third, the bivariate age-stratified analyses highlighting a greater dislike for the vaginal route of administration in younger women was purely investigative, and did not control for other potential cofactors, given the small sample size. This investigation was exploratory and is meant to contribute to hypothesis generation for future more extensive end-user studies.

Overall, when considering a potential HIV PrEP formulation, participants wanted “peace of mind.” This notion appeared to cover diverse features of the physical product, its use, and the social context depending on women’s specific circumstances, but included duration of protection, reliability, low user burden, and discreetness. Reversibility, which decreased safety concerns—together with familiarity with similar

products—mitigated uncertainty about new formulations and also contributed to anticipated peace of mind. Multiple factors played into potential users' considerations for preferred formulations, emphasizing how a suite of options for prevention might best respond to women's needs and wants.

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Address correspondence to:
 Ariane van der Straten, PhD
 Women's Global Health Imperative
 RTI International
 351 California Street, Suite 500
 San Francisco, CA 94104

E-mail: ariane@rti.org