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ORIGINAL PAPERS

Preferences and Acceptability of Vaginal Delivery Forms for HIV Prevention Among Women, Male Partners and Key Informants in South Africa and Zimbabwe: Qualitative Findings

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Abstract

The attributes of an HIV microbicide may affect its acceptability, uptake and use. Quatro, a clinical study with a qualitative component, was conducted to elicit input from end-users and key informants (KIs) on four different placebo vaginal microbicide delivery forms; fast dissolving insert, ring, film and gel. In-depth interviews and focus group discussions were conducted with young women, their male partners and KIs, to explore acceptability and preferences of the four placebo products, with the intention of improving product attributes, adherence, and consequently, long term effectiveness. None of the four microbicide delivery forms stood well above others as the most preferred. Product attributes; long-action, ease of use, invisibility, female initiated and non-interference during sex were favourable in both countries. Despite preference for the long-action, on-demand products were the most liked by women. Qualitative data from the Quatro study provided rich feedback on specific attributes important to the acceptability of four HIV prevention product platforms currently in development, enabling more informed and guided product development efforts moving forward.

Keywords Vaginal microbicide delivery forms · Facilitators · Barriers · HIV prevention · sub-Saharan Africa

Background

Young women in sub-Saharan Africa continue to be at high risk of HIV infection, with limited options for HIV prevention [1]. Large clinical trials and demonstration projects are being conducted to investigate safety and effectiveness of new technologies such as dapivirine vaginal rings and injectable cabotegravir for HIV prevention in an effort to expand the options available for women to protect themselves against HIV [2–5]. Data have consistently demonstrated that investigational and approved products must be used correctly to provide effective protection [6]. However, results from previous studies have indicated that low product adherence is one of the major challenges limiting the effectiveness of new methods for HIV prevention [7–9]. Among explanations of participant product non-use in HIV prevention trials is non-acceptability of specific product attributes, for example, concerns about ring size and firmness and gel wetness [10, 11]. Additionally, there is strong evidence that male partners and health care providers influence women's use of female initiated HIV prevention methods [12–14].

In Quatro, a mixed methods acceptability study, results of the main clinical component showed that choice of product varied significantly by country as more Zimbabweans chose the film whereas more South Africans chose the insert but overall there was no clear winner among the products [15]. A qualitative component of the Quatro study was conducted

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to complement the main clinical study with additional perspectives about the four different vaginally delivered forms for HIV prevention (placebo versions of an insert, ring, film and gel) from female clinical study participants, male partners, and key informants (KIs). This was one of the first studies to qualitatively gather input on these products from future end-users and KIs, with the aim of informing product development to optimise future acceptability and adherence.

Methods

Study Design and Setting

The Quatro Study was conducted between June 2016 and June 2017, in Chitungwiza, Zimbabwe and Durban, South Africa. Two hundred healthy, HIV negative, non-pregnant, HIV prevention product-naive and sexually-active (defined by vaginal intercourse at least 4 times per month in the past 3 months) women, between the ages of 18 and 30, were enrolled in the clinical component of the study at the two sites. They were asked to try four placebo forms of vaginally inserted ring, gel, film, and insert, in randomly assigned sequences. The placebo products used in Quatro were modeled after products in development: tenofovir/levonorgestrel intravaginal ring, tenofovir gel, tenofovir film, and tenofovir alafenamide fumarate/elvitegravir topical insert. In this study, the ring was to be worn monthly, the other three products were designed for pre-coital use. After trying each of the four products at least once per week for one month, women were asked to choose and consistently use their preferred product for the full fifth month of the study. At exit visit, all women were asked for permission for study staff to contact their male partners to invite them to a focus group discussion (FGD).

Qualitative Component Study Participants

In the qualitative component of the study, the method of data collection was mainly determined by the population group; women and their male partners were invited to take part in FGDs, while KIs participated in in-depth interviews (IDIs).

After the completion of the five months of product use, an oversample of 78 women were randomly selected after stratifying by their product of choice from the clinical study. Out of the 78, 40 women, across the two sites, Durban, South Africa (N = 20) and Chitungwiza, Zimbabwe (N = 20), were invited to participate in an FGD. A total of five female FGDs were conducted. Potential qualitative participants were contacted in the order in which their identity numbers appeared on the random selection list until the target number for FGDs was met. Nine selected participants were contacted/attempted to be contacted but not enrolled because they had migrated to neighboring countries, were not reachable or had work commitments.

Seventeen male partners of the women who participated in the clinical component of the study also took part in the qualitative component, (Durban, South Africa (N = 4) and Chitungwiza, Zimbabwe (N = 13)). Men who were aged 18 or older, willing and able to provide informed consent, and fluent in one of the languages used in the study were eligible for the study. Only male partners of those women who had provided permission were contacted by study staff and invited to take part in an FGD. In Durban, an insufficient number of men were willing and available to participate in an FGD, therefore IDIs were conducted instead.

Twenty-four KIs purposively selected from job categories including health care providers, pharmacists, Department of Health representatives, and clinical trialists, were recruited by the study staff and 12 were enrolled at each of the two sites. Eight KIs declined to participate and the main reasons for this were unavailability, heavy workload, or perceptions that they were not the appropriate person to be interviewed. IDIs with KIs were held before and during the Quatro clinical study, followed a semi-structured guide and included presentation of products samples to inspect and handle.

During study visits, each participant provided written informed consent, completed a demographic questionnaire and participated in either an IDI or FGD.

Measures and Analysis

The IDIs/FGDs were conducted by trained, experienced interviewers using a semi-structured guide.

The main topics covered in the IDIs and FGDs with women from the clinical study and their male partners were their experiences in the study, acceptability of study products, male partner knowledge of product use, effect of product use on sexual behavior, influence of male partners on product use, recommendations for future product packaging and product messaging. The women and male partners were asked to identify one product they most and least liked, and these results were manually tabulated, and reasons for preferences explored.

Interviews with KIs focused on health service delivery factors that could influence uptake of the HIV prevention products and adherence for young people, their attitudes towards the products and what they thought the young women would like or would not like about the products. The KIs were asked to rank the four delivery forms in-order of preference from 1 to 4, with 1 representing the most preferred.

During the interviews with the women, male partners and KIs, product prototypes of all delivery forms were handled and discussed (Fig. 1). A product education video was shown only to women and male partners.

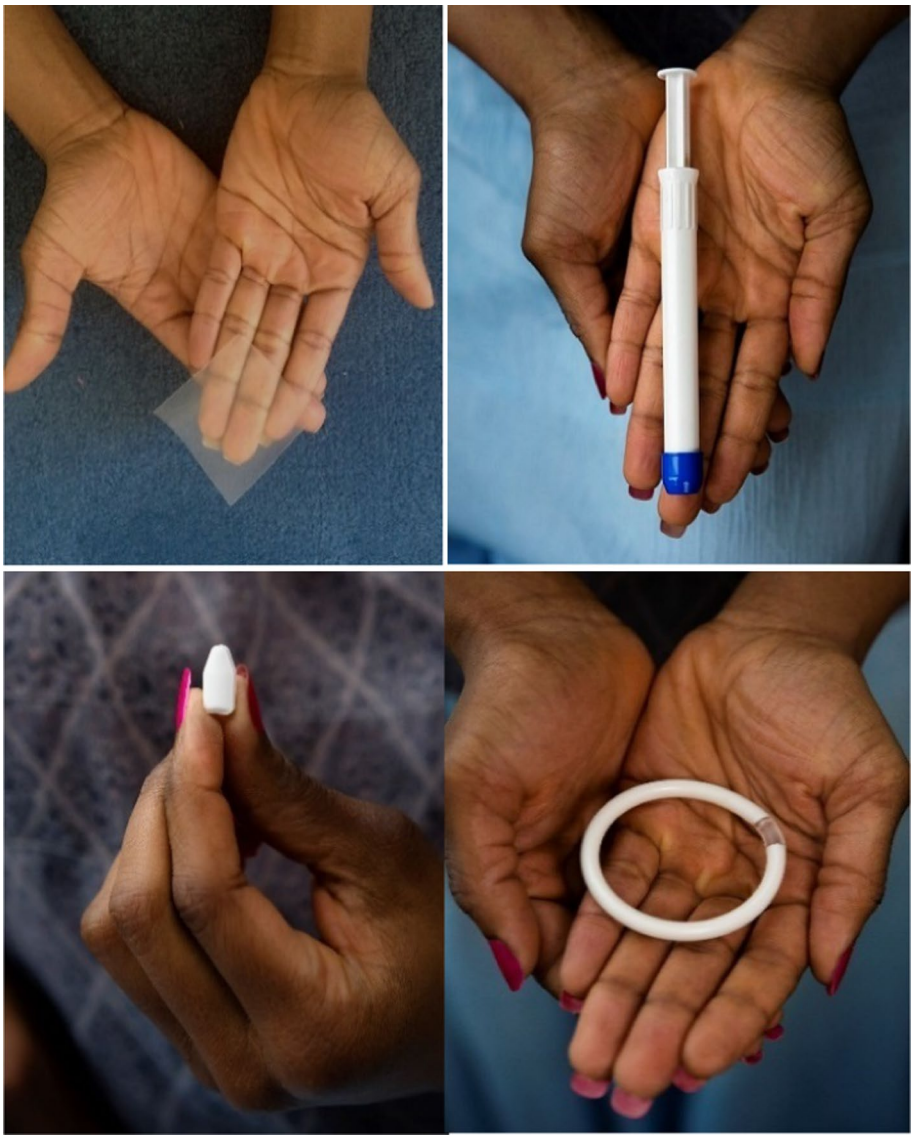


Fig. 1 Quatro study products. Clockwise from top left: vaginal film, vaginal gel (inside applicator), vaginal insert, polyurethane vaginal ring

We compared the views of the women who took part in the qualitative component to those of the men and KIs, and compared the findings between the two countries, to identify any differences and similarities.

FGDs and IDIs were conducted in English or a local language, audio-recorded, transcribed and translated into English. The audio recordings were not available for one IDI and one FGD and detailed notes were written in lieu of a transcript. All transcripts (and notes) were coded by two analysts using Dedoose, a web-based software for qualitative analysis. Regular inter-rater reliability tests were conducted to identify any differences in coding and all discrepancies in coding were resolved by consensus. For the women and male partner IDIs and FGDs, coding reports were used to investigate participant perceptions of the Quatro delivery forms based on use experience. Code reports were run for the following codes: barriers, facilitators, effect on life, preferences, side effects, and use attributes.

Results

The characteristics of the analytic sample (N = 82) are presented in Table 1. The women's median age was 24 years (range 19–30), 70% completed secondary school, 33% earned their own income. Fifteen percent were married/living with their partner in South Africa versus 95% in Zimbabwe. No differences were noted between this qualitative sample and the 200 female participants who took part in the quantitative component of the study [15]. The male partners' median age was 30 years (range 20–50), 76% were from Zimbabwe, 88% completed secondary school, and 77% earned income. All males in Zimbabwe were married to the

Table 1 Demographics: female participants, male partners and key informants

Female participants	South Africa		Zimbabwe		Total	
	N	(%)	N	(%)	N	(%)
Total	20	(100)	20	(100)	40	(100)
Median age, years (range)	23.5	(19–30)	25	(20–29)	24	(19–30)
Married or living with partner	3	(15)	19	(95)	22	(55)
Completed secondary school	14	(70)	14	(70)	28	(70)
Own income	4	(20)	9	(45)	13	(33)
Contraceptive methods ever used						
Male condom	19	(95)	10	(50)	29	(73)
Female condom	1	(5)	1	(5)	2	(5)
Pills	3	(15)	17	(85)	20	(50)
IUD	1	(5)	0	(0)	1	(3)
Implants	3	(15)	10	(50)	13	(33)
Injectable	16	(80)	8	(40)	24	(60)
Vaginal products used in past 3 months						
Tissue, toilet paper, cloth or cotton	2	(10)	3	(15)	5	(13)
Tampon	3	(15)	0	(0)	3	(8)
Male partners						
	South Africa		Zimbabwe		Total	
	N	(%)	N	(%)	N	(%)
Total	4	(100)	13	(100)	17	(100)
Median age, years (range)	28.5	(20–33)	31	(24–50)	30	(20–50)
Completed secondary school	3	(75)	12	(92)	15	(88)
Earns an income	2	(50)	11	(85)	13	(77)
Relationship with Quatro female participant						
Wife	0	(0)	13	(100)	13	(77)
Primary partner, not married	4	(100)	0	(0)	4	(24)
Aware of Quatro product used						
Film	2	(50)	8	(62)	10	(59)
Gel	2	(50)	10	(77)	12	(71)
Ring	4	(100)	11	(85)	15	(88)
Insert	1	(25)	9	(69)	10	(59)
Key informants						
	South Africa		Zimbabwe		Total	
	N	(%)	N	(%)	N	(%)
Total	12	(100)	12	(100)	24	(100)
Median age, years (range)	45.5	(31–62)	38.5	(34–56)	41	(31–62)
Female	11	(92)	9	(75)	20	(83)
Primary role(s)						
Provide services directly to clients	6	(50)	12	(100)	18	(75)
Supervise staff or other managerial	9	(75)	11	(92)	20	(83)
Current job function(s)						
Doctor	2	(17)	0	(0)	2	(8)
Nurse	5	(42)	9	(75)	14	(58)
Medical officer	1	(8)	0	(0)	1	(4)
Counsellor	4	(33)	8	(67)	12	(50)
Pharmacist	4	(33)	1	(8)	5	(21)
Researcher	5	(42)	1	(8)	6	(25)

Table 1 (continued)

Key informants	South Africa		Zimbabwe		Total	
	N	(%)	N	(%)	N	(%)
Type(s) of clients served						
Adult women	12	(100)	11	(92)	23	(96)
Adult men	7	(58)	10	(83)	17	(71)
HIV/AIDS patients	11	(92)	10	(83)	21	(88)
Family planning clients	11	(92)	9	(75)	20	(83)
Adolescent girls (age 12–18)	12	(100)	11	(92)	23	(96)
Adolescent boys (age 12–18)	6	(50)	*8	(67)	14	(58)
Children	6	(50)	6	(50)	12	(50)

female participant, whereas in South Africa none were married to the female participant. The KIs' average age was 41 (range 31–62), 83% were female, 75% provided services directly to clients, and 96% worked with adult women.

The quantitative preference ranking of each product, and the attitudes expressed by women, male partners and KIs is presented below, by product. In general, likes and dislikes centered around issues related to product duration, impact on sex, method of insertion, and discreetness.

Film

The film was the most liked or preferred product chosen by this sample of women in Zimbabwe and KIs in South Africa (Tables 2 and 3). One reason for preferring the film related to its perceived effect on the vaginal state. Some participants reported that the film tightened the vagina and enhanced sexual pleasure. A Zimbabwean woman's narrative below reflects the general perspective in that country that men prefer dry/tight sex and the female partner's desire to meet this expectation. It also highlights the underlying concerns in Zimbabwe about male infidelity, which may arise in marital relationships if the vagina is loose/wet, and how the film could help to promote faithfulness among married couples:

> *I think most women will prefer the film. Why I say that, it is because all us women here who are married, some of us have got many children, right – After having children, our vagina loosens, it will not remain as if we are still virgins. So our husbands will end up being fed up by our looseness. That is when you see men going to propose love to a form 3 school going child (~15years) because he still loves that vaginal tightness. That is what he wants. So the film is good because if you insert it, you shrink back to having that vaginal tightness that is being followed up by men, one. Two, it dries all the waters, you become the cream tape [his favourite] such that he will not go anywhere.* (Zimbabwe, Female Participant, FGD2)

Similarly, a few male partners reported that the film made the vagina dry and enhanced sexual pleasure, while others liked that the film did not disturb sex. A male partner in South Africa said:

> *.. it's just that this thing [film], ...I don't know whether it makes it [the vagina] dry like nicely, ... have you seen that when you have had sex with someone and they have become wet, ending up not feeling sex... Yes. I do not know whether it is the one [referring to the film] which holds [stops] the wetness so that I can log in [meaning so he can penetrate the vagina]... Yes this [film] made her to hold the thing [to hold the vagina tightly]... (South Africa, Male partner, IDI).*

That said, some participants in both countries, including those who overall said they liked the film, complained that the film was difficult and uncomfortable to insert due to its texture and square shape with four corners. A female participant in Zimbabwe said:

> *Personally, I liked the film. But what I did not like about the film, was the issue of wrapping it on my finger to insert. It would prick me inside.* (Zimbabwe, Female Participant, FGD2)

A female participant in South Africa also voiced the same sentiments:

> *... when you are inserting, it comes out with the finger (sticks on the finger) ...[The film] It's what I liked amongst all products. But if the way of insertion, could be changed...* (South Africa, Female Participant, FGD2)

Table 2 Positive and negative attributes of product, participant type and frequency

Product	Product attributes	
	Positive attributes	Negative attributes
Film	Female initiated*** (W,MP,KI)	Difficult to insert** (W, MP, KI)
	Tightened vagina & enhanced sexual pleasure *** (W,MP)	Takes long to dissolve/disrupts sex** (W,MP,KI)
	Small** (KI)	Plastic** (KI)
	Allows barrierless sex* (KI)	Short-term use** (W,MP,KI)
	Discreet* (KI)	Method of insertion unhygienic* (W,KI)
	Doesn't disturb sex*(W,MP)	Scratching corners during insertion* (W,KI)
	Easy/painless to insert**(W,KI)	Made vagina too wet* (W)
	Dissolves* (W,KI)	
Insert	Female-initiated*** (W,MP,KI)	Made vagina wet/reduced sexual pleasure** (W)
	Small & easy to use** (W,MP,KI)	Short term use** (W,M,KI)
	Tightened vagina/ enhanced sexual pleasure* (W,MP,KI)	Stigma- Packaging & pill-like form similar to ART* (W, KI)
	Familiarity- looks similar to pills*(KI)	Method of insertion may cause infection* (W,KI)
	Discreet*(KI)	Too small to insert properly* (W,KI)
	Easily dissolves* (KI)	
	Shape shows how to insert it*(W,KI)	
	Allows barrierless sex* (KI)	
Gel	Lubrication improves sex*** (W,MP,KI)	Excess lubrication of the vagina decreased sexual pleasure ****(W,MP,KI)
	Use of applicator makes insertion hygienic & painless*** (W,KI)	Short term use** (W,MP,KI)
	Female-initiated***(W,MP,KI)	Excess lubrication makes gel noticeable & raises mistrust* (W, MP, KI)
	Sex feels normal*(W,MP)	Bad odour* (W, KI)
	Allows barrierless sex* (KI)	Feels cold when inserting* (W)
	Discreet* (KI)	Gel leaks messy/compromise protection* (KI)
		May introduce infection into the vagina* (KI)
		Inserting applicator could be uncomfortable* (KI)
		Gel applicator bulky, storage & disposal challenges* (KI)
		Gel application requires too much privacy *(KI)
Ring	Worn continuously for a month****(W,KI)	Can be felt/disturbs sex**** (W,MP,KI)
	Female initiated***(W,MP,KI)	Ring too big, hard & scary**** (W,MP,KI)
	Allows barrierless sex/ Enhances sexual pleasure**(W,MP,KI)	Difficult to insert properly **** (W,MP,KI)
	Not felt during sex/ Did not disturb sex*(W,MP,KI)	Caused vaginal wetness* (W)
	Easy to insert/remove *(W)	Method of insertion unhygienic/uncomfortable* (W)
	Discreet* (KI)	Ring invaded male partner's territory*(W,MP,KI)
		Foreign object stays too long in the vagina* (KI)

W women, *KI* key informants, *MP* male partners

*Total number of participants making each statement

* = 1–10

** = 11–20

*** = 21–30

**** = 31–40

For some participants in South Africa, the difficulty and discomfort experienced with insertion of the film appeared to supersede the benefit of vaginal dryness:

> *It's the only product that I could say I didn't like, because I first struggled with insertion and it is also poking. So, I didn't trust it anymore. It was as if it was coming out, I had not inserted it well, it didn't go straight to where it should be. Ay! No! even though I feel the dryness but…* (South Africa, Female Participant, FGD2)

Table 3 Number of women and male partners who selected product as "most" and "least" liked, by country and Key Informants' ranking of products

	Zimbabwe (N = 33)		South Africa (N = 24)		Total (N)
	Women (n = 20)	Male Partners (n = 13)	Women (n = 20)	Male Partners (n = 4)	
Most liked product					
Gel	5	3	6	2	16
Ring	5	3	5	0	13
Insert	1	6	6	2	15
Film	9	1	3	0	13
Least liked product					
Gel	4	4	0	1	9
Ring	8	8	13	2	31
Insert	7	0	0	0	7
Film	1	1	9	0	11

Key informants' ranking of Quatro products

Product	Zimbabwe (N = 12)						South Africa (N = 12)					
	Tally of rankings 1–4 (1 = Most preferred)											
	1	2	3	4	Average score	Overall order of preference	1	2	3	4	Average score	Overall order of preference
Ring	8	1	3	0	1.58	1	3	1	3	5	2.83	4
Film	0	7	2	2	2.42	2	4	4	2	2	2.17	1
Insert	3	3	4	2	2.42	2	3	4	4	1	2.25	2
Gel	1	1	3	8	3.58	4	2	3	3	4	2.75	3

Some participants in Zimbabwe expressed that they did not like using their fingers to insert the film and indicated that use of an applicator would have been preferable:

> *I did not have problems with the film but my challenge is on the use of fingers. On inserting. My fingers should not just be inserted inside. The film should have an applicator....* (Zimbabwe, Female Participant, FGD2)

In addition to insertion challenges, some participants in both countries complained that once inserted, the film took long to dissolve. A female participant in South Africa said:

> *But the problem I had was that it took long to melt and ended up being just a lump which I don't know, a hard one. Such that when I feel it, oh no, the thing is still there, it's hard.* (South Africa, Female Participant, FGD3)

A concern that the KIs had that was not shared by women in the study, was not believing that the film protects, due to the perception that it is made from plastic. Though KIs stated that the film appeared easy to insert, many women experienced insertion challenges when using the film.

Gel

In South Africa, the men and women indicated that the insert and the gel were the most liked products whereas in Zimbabwe, they rated the gel second to the film, even though the KIs in both settings thought it would be last or second to last due to concerns about gel application and privacy during insertion (Tables 2 and 3).

In contrast to the film, participants described increased vaginal lubrication while using the gel. Some participants complained that it caused excessive vaginal wetness, reduced sexual pleasure and caused disapproval for the same reason that the "dryness" associated with the film was considered favourable. A female participant in South Africa said:

> *I don't like something that makes me wet in the vagina. You know gel made me wet, I couldn't even feel what I was doing during sex because something that makes me wet in the vagina when I'm having sex... No, I don't feel right.* (South Africa, Female Participant, FGD2)

The vaginal lubrication resulting from gel use caused infidelity concerns for female participants from South Africa, and for male partners from both countries. A male participant in Zimbabwe said:

So, gel increases wetness, which causes you to think, if you are someone who thinks a lot, you might think that my wife -- if you had not seen her applying the gel. You might suspect that your wife might have wanted to have sex with someone else… Because she will be already wet… When she would have just applied the gel. At one point I asked why her vagina was now always wet when it's supposed to get wet when we are about to have sex. (Zimbabwe, Male Partner, FGD2)

Contrary to some participants' perceptions that the gel caused excess wetness, other participants liked that the gel provided vaginal lubrication and said it improved sex. A female participant in Zimbabwe said:

W*henever I would insert the gel, I would actually fantasize my partner already inside… So haa, gel was just good.* (Zimbabwe, Female Participant, FGD2)

Despite initially having concerns about the gel, the women and their male partners discussed a unique facilitator to gel use: the applicator. Female participants from both countries described that use of an applicator made insertion of gel easy. Male partners and female participants in Zimbabwe also discussed that using an applicator for product insertion was more hygienic compared to use of fingers. A female participant in Zimbabwe discussed how use of an applicator influenced her decision to choose the gel as her most liked product:

…it is smart. You don't touch your vagina, you don't dip your fingers into your vagina. You had an applicator. (Zimbabwe, Female Participant, FGD2)

Once inserted, a few participants in South Africa reported that the gel felt cold. A female participant in South Africa said:

The problem is that it is cold when you have inserted it, it is cold inside here. It is like you have inserted something like a Vicks [Brand name for a nasal decongestion ointment with menthol] I don't know but it is cold. (South Africa, Female Participant, FGD2)

The KIs had predicted that the added lubrication of the gel would be a barrier to use, citing leakage problems, men's preference for dry sex and the fear that it would reduce sexual pleasure. When asked about what would make women not want to use the gel, a key informant in Zimbabwe said:

Lubrication. More lubrication…More fluids that becomes messy. (Zimbabwe, Health care provider, IDI)

Only a few indicated that it would be a positive attribute for women with vaginal dryness, partners with large penises, or simply for increased pleasure. Although not common, the concern raised by the KIs that leakage may compromise the effectiveness of the products was also observed among the women. One participant in Zimbabwe said*:*

I think most people like injectables because like myself if I get an injection I know that the drug has gotten into my blood. Maybe this one if I insert it like these ones it may start causing vaginal fluids. I would start thinking that those vaginal fluids, maybe it [the drug] is coming out and wasn't absorbed into the system. (Zimbabwe, Female Participant, FGD1)

Similarly, to some of the women, KIs overall preferred the concept of an applicator, although they were concerned that women may not insert the applicator deep enough which may lead to leakages thereby compromising the level of protection from the gel.

Insert

The insert was one of the two most preferred products among women in South Africa, men in Zimbabwe, and KIs in both countries (Tables 2 and 3). Some participants in both countries found the insert easy to use due to its small size and shape. Ease of use was described as not causing pain during insertion, quick to insert or dissolving completely. A female participant in South Africa said:

Ay, the insert is alright…It doesn't waste any time, it's nicely small, it's quick to insert, it is quick to dissolve. (South Africa, Female Participant, FGD2)

Additionally, some participants explained that the insert enhanced sexual pleasure through tightening the vagina, a few however expressed that it provided lubrication to the vagina. A female participant in South Africa said:

I liked it because when it has dissolved it produced that wetness and then it created that more sex pleasure. (South Africa, Female Participant, FGD2)

A male participant in Zimbabwe who preferred dry sex said:

Personally I prefer vaginal dryness… I want it to feel natural… So when we use the pill [meant insert] it removes that wetness that will already be there, since the vagina is always wet … (Zimbabwe, Male Partner, FGD2).

Contrary to some participants' perception that the insert tightened the vagina, some women in Zimbabwe complained that the insert caused significant discomfort due to vaginal wetness which made sex unpleasurable to both male and female partners. A participant in Zimbabwe explained how the vaginal wetness she experienced due to use of the insert

negatively affected sexual pleasure, reduced frequency of sex and generated feelings of embarrassment:

Because as soon as you start having sex, he would say let's wipe away this water. So, you will be very embarrassed. So you will not even enjoy sex because you will be very embarrassed
(Zimbabwe, Female Participant, FGD1).

Health care providers expressed interest in promoting the insert because of its simplicity which they thought would make it acceptable to women. They further explained that the small size, dissolvability, discreetness, ability to self-administer and ease of use would make the insert desirable for women. A few health care providers discussed a pre-existing familiarity with vaginal suppositories in their community for treatment of STIs and thought this underlying familiarity with the delivery method would facilitate introduction of a vaginal insert for PrEP for their patients.

A health care provider in Zimbabwe said:

Women have always been inserting suppositories and the like… so it is easy to use.
(Zimbabwe, Health care provider, IDI).

Ring

Of the four study products, the ring appeared to be the least popular among the women and the male partners in both countries (Tables 2 and 3). The KIs in South Africa had diverse preferences, but the average scores indicate that the ring was the least preferred product. Conversely, most of the KIs in Zimbabwe ranked the ring as their first choice.

Some female participants in both South Africa and Zimbabwe and only male participants in Zimbabwe, liked that the ring can be worn continuously for a month which makes it easier, more convenient and less burdensome to use compared to the other on-demand products. Both male and female participants discussed advantages of having the ring in situ all the time, including not having to remember to use it every day and carry it when travelling, the convenience that they could have sex anytime and the ever-ready protection against HIV. A female participant in Zimbabwe said:

I loved the ring because you just wear it once… It just stays in there all the time… (Zimbabwe, Female Participant, FGD2)

The long-acting characteristic of the ring was found appealing even to some women who overall said they did not like it. A female participant in South Africa said:

I also didn't like the ring but what I liked about it is that you insert it once and it stays. (South Africa, Female Participant, FGD2)

More than half of the male and female participants chose the ring as their least liked product, citing that they felt it during sex and that it disturbed sex. This negative effect of the ring appeared to override the benefits of having it in situ continuously. A female participant in South Africa described how the disruptive effect of the ring on sex could ruin the sexual experience:

Ay the ring, while I am busy on this side [having sex] I am also thinking that this thing could happen to come out. You know, this thing is moving here. No, it is disturbing me. So, it is better not to use it … because it is disturbing the plans [sex]. My mind is somewhere else and his mind is somewhere else, ay. It's just bad. (South Africa, Female Participant, FGD2)

A female participant from Zimbabwe indicated other factors participants considered more important than just the long-acting attribute of a product. She said:

I liked the ring because it is only inserted once… But I did not continue to like it because of partner. I feel the ring should be increased in size [the ring diameter] because his organ [penis] would be stuck tightly and get bruised. (Zimbabwe, Female Participant, FGD1)

Many women found the ring difficult and uncomfortable to insert properly and felt burdened to keep checking and pushing it up into the vagina. The narrative below from a participant in Zimbabwe illustrates how the difficulty with correct insertion of the ring and the discomfort associated with feeling it coming out influenced the participants' perception of the ring:

*Personally, I did not like the ring because I felt a lot of discomforts. To the extent that sometimes I would feel it coming down and it would be about to come out. When I go to the toilet, wash my hands and do this [try to feel the ring], I would feel it on the opening of the vagina. So I personally did not like it. (*Zimbabwe, Female Participant, FGD1)

Indeed, the majority of participants complained that the ring was too big, hard and scary to insert into the vagina for a long time. A female participant in South Africa said:

It is scary if you are a woman, to have something sitting here in your womb, ay no shame I say "thank you" to it [meaning she is not interested in the ring], really. (South Africa, Female Participant, FGD2)

A male partner from South Africa, who felt that the ring is too big, reported that he could not penetrate deep into the vagina because it blocked him. He said:

Mmm, it was bad because it was here like in the front you know, you end up not reaching [penetrating] far. (South Africa, Male Partner, IDI)

Similar to comments about the film, the women mostly in Zimbabwe expressed dissatisfaction that the ring did not have an applicator. A quote below from a participant in Zimbabwe reflects the concerns that some people have about touching the vagina and how use of an applicator to insert the ring might overcome this and improve ring placement:

If it were possible to find an applicator for the ring just like on gel, where an applicator is used to push it. Because someone might feel disgusted … to insert her fingers in there [vagina] or someone will have a problem with inserting using her fingers down there… If she inserts with that applicator, it should just sit, no movements to be experienced after it has been placed. (Zimbabwe, Female Participant, FGD1)

The women in both countries, including those who felt that male partner disclosure was important, expressed interest in an HIV prevention method which is invisible so that they have a choice to use it secretly. The women discussed the circumstances in which they may prefer to use HIV prevention products without the knowledge of their partners. A female participant in Zimbabwe said:

It is very important for the product not to be felt. If we want to analyze, most women are suppressed in homes. The husband will be going out there for prostitution but at the same time refusing condom use with his wife… I will just look for my product and use it quietly protecting myself alone. (Zimbabwe, Female Participant, FGD1)

However, to most women, the attributes of the ring could not permit women's preference to keep its use a secret, resulting in involuntary disclosure. A female participant in Zimbabwe said:

You will be knowing your person [partner], he will be very talkative. So you would have decided to do your things secretly. But the ring was discovered. (Zimbabwe, Female Participant, FGD2)

A male partner in South Africa also commented that the size of the ring makes it difficult for the woman to use without the knowledge of the male partner:

Maybe, if the size can be reduced, because it seems like it is too big maybe. Ja, so that even if it is a woman whose partner doesn't know that she is using these products, so that he won't find out. Because you can feel it. (South Africa, Male Partner, IDI)

A view unique to male partners in both countries suggested that men consider the vagina as their territory and are jealous about vaginal products, particularly the ring because it stays in the vagina. An illustrative quote below from a male partner in South Africa reflects the issue of "vaginal ownership" and power in relationships, where men see themselves as decision makers in sex:

Mm I don't think the ring is right because it's… it's something that you insert in the vagina you know. So, as men we are sceptical of things related to the vagina things like that, you find that… I feel something. After that you will explain to me about something that is inside you, so I wouldn't recommend the ring as the right thing because it is touchable inside, you know [meaning his penis touches the ring when having sex]… so something related to the vagina, we as men will not allow something like that, or I should just say I would not allow something like that... (South Africa, Male Partner, IDI)

A male participant in Zimbabwe considered the vagina as a no-go-area for the ring:

I was not comfortable with using it [ring]… because my mind already - registered that this thing is being inserted where it's not supposed to go. (Zimbabwe, Male Partner, FGD2)

A female participant in Zimbabwe described inserting things into the vagina as messing around with her male partner's territory, which motivated her to use the products secretly:

Especially me, I had not told my partner that I am inserting things down there, because he does not even want to hear that you are messing around with his area (participant's vagina). (Zimbabwe, Female Participant, FGD2).

As reported by women, the KIs liked that the ring offers protection for a month and women do not have to worry about inserting a product within two hours of sex. One health provider from Zimbabwe said:

Because there are no interruptions, no hassles, it is always there. Because they might forget to reinsert [the other three products]. (Zimbabwe, Health Care Provider, IDI).

A key informant in South Africa also expressed the same sentiments:

...I like it. I think it is very innovative... Well the fact that they put it in. As long as it's comfortable it would be there. They wouldn't have to worry about it. It's there for a month and you know the medication is just

ehm being diffused out. (South Africa, Community Stakeholder, IDI)

On the other hand, KIs expressed some of the same concerns that the female participants had voiced about the ring's large size and stiffness. A health care provider in South Africa said:

...It's huge... And hard... Uncomfortable... Perception is everything. I wouldn't use that [ring]... And it would be hard for me to say someone must use that. (South Africa, Health care provider, IDI)

Due to the ring's size and firmness, they anticipated that women would be afraid of the ring and would think its insertion would be painful. The KIs were also concerned that the ring may not stay in place or could be felt by the male partner during sex and cause discomfort. Some KIs wanted the ring to last longer and others thought women would be sceptical of having a foreign object in their vagina for an entire month, a concern that was voiced by some of the women.

All Products: Ring, Gel, Film and Insert

Several themes pertained to all of the vaginal study products, and tended to reflect broader societal norms, as opposed to specific product features. These included the concept of a female-initiated HIV prevention method, and how disclosure and gender norms influence method use. Additionally, there were concerns about how vaginal insertion could have long-term negative health consequences such as reproductive health cancer.

Male and female participants in both countries appreciated that the products they tried in the Quatro study were female initiated, such that women's protection did not rely on male cooperation. A female participant in South Africa said:

It's just that men, like this one of mine; does not want a condom. So when I come, already having inserted my things, no it is alright, I am already protected. (*South Africa, Female Participant, FGD3*).

A male participant in Zimbabwe discussed multiple factors influencing women's risk of acquiring HIV including the power dynamics in sexual relationships limiting women's ability to negotiate safe sex and how a female- initiated method may empower them to have control over their health:

I think that if women use… these products by themselves as a way of preventing HIV and AIDS… It's good in the sense that they are the ones on the receiving end, they do not have bargaining power like we have us men… So if she protects herself it would be good for them. Looking at some of our friends who go to bars…They earn a living through that… Having sex with men… So I might be in a state of drunkenness… I might say to a woman, "no take this $100 then I have unprotected sex with you." You see right. Because she wants money she would just say it's okay. But if she is the one using protection… (Zimbabwe, Male Partner, FGD2)

However, some male partners strongly felt that male-partner consent is required for women to use female-initiated products for HIV prevention, else they would not be supportive. If partners are given knowledge up front, they will be better positioned to provide "consent" for use. One male participant in Zimbabwe expressed that he felt cheated when he discovered that his partner used the film without his knowledge:

… at times like I said, when we used the film I had to say 'there is something inside…' Yes so that can cause trouble and might cause us to not accept them because I would view it as being cheated, doing things behind my back. (Zimbabwe, Male Partner, FGD2)

The issue of partner disclosure and consent was significantly influenced by the type of relationship. Most of the women in South Africa were not married and reported use of study products without the knowledge and consent of their male partner, whereas the majority of the female participants in Zimbabwe were married and said that male partner knowledge and approval were important for product adherence. The narrative of a married female participant in Zimbabwe reflects how relationship dynamics could be an important factor in partner disclosure and acceptability of female-initiated HIV prevention methods:

I disclosed [product use] because like myself I have a husband right… I am given products to go and use at home. If I don't disclose, it would be a problem because he would say, 'What is it that you have in this house?' Or, 'What is it that you are inserting?'… So disclosing was important for me because I would use my things [products] freely. (Zimbabwe, Female Participant, FGD2)

A male partner in Zimbabwe described how he influenced the product choice of the female partner during the study:

Then when the four months lapsed, that is when she came here and was asked what she would prefer on all the products that she used… Then she said my husband liked the pill [insert]… Then we used the pill [insert] again. (Zimbabwe, Male Partner, FGD2)

In addition, a concern about vaginal products causing side effects like reproductive cancers was common among KIs, particularly the health care providers, and the women. This fear could be linked to the ongoing health education

messages discouraging women from inserting things into the vagina, as one of the health care providers in Zimbabwe expressed:

And cervical cancer, that we teach them that, "don't insert things in the vagina." Then maybe they will fear side effects if there are any. (Zimbabwe, Health care provider, IDI)

A female participant in Zimbabwe echoed the same concern:

I think most women will not choose Quatro products. They do not want to insert things down there because they are afraid of having cancer. (Zimbabwe, Female Participant, FGD2).

Like women, the KIs also found the use of fingers for insertion undesirable, citing a concern that it introduces infection into the vagina. A health care provider in Zimbabwe said:

Infections… Since it is something that is inserted…Yes, we don't know how they will handle it during insertion. Won't they end up with vaginal infections? (Zimbabwe, Health care Provider, IDI)

KIs in both countries expressed worry that the general aversion to touching one's vagina would prohibit women from using the products (as noted in the results above). A health provider in Zimbabwe said:

Young people are not comfortable to have anyone touch or anything that goes through the vagina… people start thinking about uhm- -, what if I am introducing a foreign thing in my vagina… Things like cancer. (Zimbabwe, Health care provider, IDI)

Despite having initial concerns about the products, health care providers expressed an overall interest and willingness to recommend, provide, and promote use of the four products if they protect women against HIV and become available. They anticipated that some of the concerns they had would disappear with participant education, product use counselling and actual use.

Discussion

In the Quatro study, we explored acceptability, preferences, end-user experiences and effect on sexual behaviour of the four placebo products among young women, their male partners and KIs to better understand how to improve microbicide product development, including optimizing attributes and the end-user experience, and ultimately, uptake and adherence.

In this study, preference for a long-acting attribute of a product was noted. These results support findings from previous studies where participants expressed interest in products offering long-term protection [16]. However, results of this Quatro qualitative research indicate that participants considered factors other than long-term use as more salient. Overall, the ring had the highest number of participants who identified it as their least liked product, despite the fact that some women and health care providers favoured its long-acting attribute. Participants found other characteristics of the ring such as the big size, stiffness and negative effect on sex and sexual pleasure undesirable. As with other products, participants had suggested modification of some of the attributes of the ring to improve acceptability and use, such as provision of an applicator and reducing the size. However, with experience and use over time, the ring also had the greatest positive change in ranking in the larger quantitative study [15].

Some participants discussed the dryness of the vagina during sex as a benefit of using the film. However, similar to another study [17], these participants expressed dislike of the sharp corners and plastic appearance of the film and recommended that the shape be modified to facilitate ease of insertion. Participants who felt that the gel caused too much vaginal wetness suggested that the amount of the gel in the applicator be reduced. As new products for HIV prevention advance, product developers need to prioritise those attributes that are most likely to be acceptable to potential end-users and those likely to influence use.

Results of this Quatro qualitative study concur with the product rankings and choice in the main clinical study with a larger sample, which indicated that there was no winner among the four products and the ring was the most polarizing of the four delivery forms [15]. Similarly, product choice was significantly different by country and the film and insert were most favoured in Zimbabwe and South Africa, respectively. The results of the qualitative study complement those of the main clinical study through shedding light on some of the possible explanations for the differences in product choices between the two countries. For instance, the perception of the film tightening the vagina in Zimbabwe could be important given the higher parity, male partner's explicit preference for dry sex [18, 19], and the perception that a loose/wet vagina could imply a woman's infidelity. Similarly, the insert was favoured in South Africa because of how it changed the feeling of the vagina. This qualitative research provided women with an opportunity to indicate whether they would use any of the products in the future if available.

Participants' perspectives about study products differed, possibly due to individual preferences. For instance, while some participants reported that the gel lubricated and improved sex, others felt that it caused too much wetness and reduced sexual pleasure. The findings of this study support

the benefit of multiple options for women and data from previous studies on wet and dry sex, vaginal tightness and looseness, what men and women prefer and the reasons, as well as how this varies according to geographical settings [20, 21]. These results highlight the need to expand the options available for women to use and protect themselves from HIV.

Our findings also indicate the need to explore cultural influencers of product uptake and use, for instance touching the vagina is taboo in some cultures [22, 23] and having an applicator for product insertion could be an advantage by facilitating initial uptake.

Participants' discussions reflected the issue of power dynamics between men and women and the impact of this on decision-making around sex and covert use of products for HIV prevention. Some participants – both male and female – liked that Quatro study products are female-initiated, citing that women are at a higher risk of HIV infection compared to men and their ability to negotiate safer sex is compromised by the cultural factors and their economic dependency on men [24–26]. However, some men's desire to be involved in shared decision making in their partners' health-related matters came out strongly. The male partners expressed disapproval of having their female partners taking part in research and using products without their knowledge which supports the widespread evidence of men influencing use of female-initiated methods. This perception is further supported by the male-partners' concept of considering women's vagina as their "territory", which suggests the dominant patriarchal norms in relationships, with important consequences for women's autonomy to choose methods to protect themselves from HIV.

Similar to other studies, some of the women in this study considered disclosure of their participation and use of study products to their male partners as desirable and culturally appropriate [12]. Results from this study corroborate the view that some women may not be able to use female-initiated devices without the involvement of their male partners. However, the different relationship patterns and dynamics in these two countries might have influenced the stronger presence of male partner involvement in the use of female initiated HIV prevention methods in Zimbabwe. Male engagement in research is therefore critical in-order to support participation and product use, especially in the context of stable partnerships.

Participants' concerns about vaginal products causing reproductive cancers, corroborate results of other studies [27] and could be reflecting the possible misalignment of public health messages for cervical cancer prevention and those for microbicide use, and/or highlight the need for increased education in parallel with microbicide introduction.

Largely, KIs' predictions of what the women would like/dislike about most of the products, except regarding the actual ease of use with the film, were confirmed by the reports of the women themselves which demonstrated good knowledge and understanding of the young women they offer their services to. This highlights the usefulness of involving health care providers and other KIs early in research so that they support the on-going HIV prevention efforts.

There were limitations to this research. Firstly, only 4 out of the 17 male partners who participated in this study were from South Africa and this could be linked to the type of relationship and disclosure of product use to partners. The majority of female participants in South Africa were not married and less likely to disclose product use and invite their partners to take part in an IDI. Hence, male partners, were a highly selective group which might not be representative of a wider population. Additionally, some male participants had limited knowledge and use experience of the products which limited their ability to fully express their views about them. The women who took part in the qualitative component were randomly selected after stratifying by product of choice and this might have introduced bias in their ranking of the products. The link between preference for a delivery form and prior contraceptive experience was not analysed among the subgroup in the qualitative component but in the quantitative paper [15]; the results showed that participants who had experience with implants were more likely to choose the ring because it is long-acting. In the KIs, we did not ask directly about previous experience with microbicide research. Out of the 24 KIs, 2 mentioned involvement and 1 was known to be involved in prior microbicides studies and this experience might have influenced their views and perceptions of the four vaginal delivery forms.

Conclusion

Participants discussed the attributes they liked about the four products; vaginal gel, insert, ring and the film with qualitative results further supporting the quantitative acceptability and product preferences results previously reported [15]. However, they also expressed concerns about various product attributes, especially those of the ring, and they recommended specific modifications to improve acceptability and use. A product that is safe, long-acting, easy to use and non-interfering with sex could be more likely to be accepted and used. Participants' different experiences with and perceptions about the four products further justify the need to expand the options available for women to protect themselves against HIV. Male partners' views about female-initiated products for HIV prevention suggest the need to

scale up male partner engagement activities in future studies targeting women and the importance of involving them early enough to contribute meaningfully to the ongoing HIV prevention efforts.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures were reviewed and approved by ethics and regulatory bodies in the US (Chesapeake IRB: 00150063), South Africa (Human Research Ethics Committee of the University of the Witwatersrand (151106); Medicines Control Council (DB: N2/19/8/2)) and Zimbabwe (Medical Research Council of Zimbabwe (MRCZ/A/1988), Medicines Control Authority of Zimbabwe (B/279/5/07/2016)) before implementation.

Informed Consent Written informed consent was obtained from all the participants enrolled in the study.

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