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Performance and Acceptability of the FC2 Female Condom When Used With and Without a Silicone Placebo Vaginal Ring—A Randomized, Crossover Trial

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Background: The silicone Dapivirine Vaginal Ring 25 mg, has been developed to provide an additional HIV prevention option for women. If approved for use, women will always be counselled to use condoms when using the vaginal ring for maximum protection. This paper evaluates the compatibility of female condoms with the ring.

Methods: This was a 2-period crossover, randomized noninferiority trial. Couples in 2 sites in the United States of America were randomized to FC2 Female Condom (FC2) with and without a placebo silicone ring and asked to use 4 female condoms in each period. The primary noninferiority endpoint was the clinical failure rate during intercourse or withdrawal (self-reported clinical breakage, slippage, misdirection, and invagination). Frequencies and percentages were calculated for each failure mode and differences in performance of the 2 periods, using the female condom without the ring as reference. Noninferiority was defined using an 8% margin at the 5% significance level. Safety and tolerability were also assessed.

Results: Eighty-one couples were enrolled and 79 completed the trial using a total of 596 female condoms (297 and 299 with/without a ring inserted, respectively). Total female condom clinical failure was 14.1% and 15.7% in the presence and absence of a ring, respectively, with a difference of −2.1% (95% confidence interval: −7.8% to 3.6%), thereby demonstrating noninferiority when used with the ring. There were no differences in safety and tolerability between the 2 periods.

Discussion: Concurrent use of the placebo silicone vaginal ring had no significant effect on female condom functionality or safety outcomes.

Key Words: vaginal ring, female condom, HIV prevention

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INTRODUCTION

Both male and female condoms are promoted in sub-Saharan Africa as part of the HIV, sexually transmitted infections (STI) and pregnancy prevention strategies of The Joint United Nations Programme on HIV and AIDS.[1] There exists limited, but convincing evidence that the female condom is effective in increasing protected sex and decreasing STI incidence among women.[2] Female condoms protect against pregnancy 95% of the time when used correctly, and 79% of the time during common use.[3]

Female condoms are becoming more available in many sub-Saharan African countries, with South Africa having one of the most comprehensive female condom programs globally.[4,5] Female condoms have been made available in all South African public health sector facilities since 2014 and a national health facility survey including 3821 women, reported that 15.4% of women had ever used the female condom.[4] In Africa, both male and female condoms are distributed (often free of charge) through a range of outlets.[1] This increased promotion and access has contributed to a rise in female condom use in this region.[6,7] In a 4-country safety and acceptability trial of the dapivirine ring, 2.5% of women reported at enrolment always or sometimes using female condoms in the past 4 weeks.[8]

A silicone vaginal ring, containing 25 mg of dapivirine, a non-nucleoside inhibitor of HIV type 1 (HIV-1) reverse transcriptase, has been evaluated in 2 phase III clinical trials IPM 029(The Ring Study) and MTN-020 (ASPIRE).[9–11] Monthly use of the dapivirine vaginal ring (DVR) reduced women's overall risk of HIV-1 infection by approximately 31% compared with the placebo ring; greater risk reduction can potentially be associated with increased adherence to ring use.[10,11] If approved for use, the DVR could provide an additional HIV prevention option for women in sub-Saharan Africa where the need for woman-initiated HIV prevention is greatest. Women will always be

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counselled to use either male or female condoms with the vaginal ring for maximum protection.

Condom compatibility laboratory studies were conducted to evaluate whether dapivirine itself has any effect on the physical properties of a variety of types of male and female condoms. There are 3 major chemical components to the ring—polydimethylsiloxane rubber, silicone oil (dimethicone), and dapivirine. Silicone oils are the most commonly used lubricants applied to male and female condoms during manufacture.[12] Based on the ubiquitous use of polydimethylsiloxane silicones with condoms, it can be concluded that there is no effect of these formulation components (totalling more than 99.6% by weight of the dosage form) on condom function. The dapivirine drug substance (comprising 0.3125% by weight of the formulation) has been shown to have no impact on condom functionality when applied as a gel formulation and tested according to American Society for Testing and Materials test method standards (unpublished data available on request).

Female condoms were not recommended for use in the phase I-III vaginal ring clinical trials, therefore, no data on the concomitant use of female condoms and the vaginal ring are available. Condom function studies are conducted on all new male and female condoms to evaluate whether they function as well as existing approved devices. These trials are required for regulatory approvals and are also required if female condoms are going to be used concomitantly with another newly developed device inside the vagina.

A female condom functionality trial that assessed the functional performance of female condoms in the presence and absence of a placebo vaginal ring was conducted to determine whether female condoms and vaginal rings are compatible and acceptable to use together.

MATERIALS AND METHODS

This was an open-label, randomized, 2-period, crossover noninferiority trial, conducted at 2 research centers in the United States of America.

Study Objectives

The primary objective was to compare the functional performance of the FC2 female condom when used concomitantly in the presence and absence of a silicone placebo vaginal ring.

The primary noninferiority endpoint was the clinical failure rate during intercourse or withdrawal (self-reported clinical breakage, complete slippage during intercourse, misdirection, and invagination). Total female condom failure (total clinical failure and nonclinical breakage) was defined for the purpose of this manuscript, a definition recognized by the World Health Organization and regulatory agencies. Definitions of each failure mode analyzed are as follows:[13,14]

- Clinical breakage: Breakage during sexual intercourse or during withdrawal of the female condom from the vagina. Clinical breakage has potential adverse clinical consequences.
- Nonclinical b-reakage: Breakage noticed before intercourse or occurring after withdrawal of the female condom from the vagina. Nonclinical breakage is without potential adverse clinical consequences.
- Total breakage: The sum of all female condom breakages at any time before, during, or after sexual intercourse; and includes both clinical breakages and nonclinical breakages.
- Slippage: When a female condom slips completely out of the vagina during sexual intercourse.
- Misdirection: Vaginal penetration whereby the penis is inserted between the female condom and the vaginal wall.
- Invagination: When the external retention feature of the female condom is partially or fully pushed into the vagina during sexual intercourse.
- Total clinical failure: The sum of female condoms that break or slip, or are associated with misdirection, invagination, or any additional failure mode(s) identified in the risk assessment, which result in reduction of the female condom protective function.
- Total female condom failure: The sum of female condoms for which a clinical breakage or slippage occurs, or is associated with misdirection, invagination, or nonclinical breakage, or any additional failure modes(s) identified in the risk assessment.

Secondary Trial Objectives Were

- To assess the safety and tolerability of female condoms during vaginal intercourse in the presence and absence of the placebo vaginal ring.
- To assess user acceptability of female condoms during vaginal intercourse in the presence and absence of the placebo vaginal ring.
- To assess occurrence of the placebo vaginal ring expulsion or removal associated with the use of female condoms.

Safety was assessed through recording of adverse events (AEs; defined as any self-reported urogenital discomfort that arose during female condom or female condom/ring use that lasted more than an hour, any other urogenital or non-urogenital medical problem that could be related to female condom or the placebo vaginal ring use or any serious AE) and assessing the number, severity, relatedness, and duration of AEs by treatment period. Events occurring of an hour or less were recorded as medical events. Standard acceptability measures were collected.

Study Population

The target population was 81 urban, sexually-active couples in the USA who were either novice or experienced users of female condoms. The couples were recruited from 2 research centers in California. Key inclusion criteria included:

- Mutually monogamous healthy heterosexual couples; current relationship ≥3 months; who could give written informed consent and were willing to comply with the trial procedures;
- Age ≥18 and ≤45 years (women) and ≥18 and ≤55 years (men) at time of the screening visit;
- Not at risk of pregnancy, that is, female is surgically sterile, using an intrauterine device, or using effective hormonal

contraception, or had a vasectomized partner. The use of vaginal contraceptive rings was not allowed;
- Low risk of acquiring HIV infection;
- Sexually active and agree to have at least 8 acts of penile–vaginal intercourse using a study condom over 2 periods of up to 6 weeks each;
- Agreed to use only the female condoms and study lubricant provided by trial personnel, and not to use male condoms and nonstudy lubricants during the trial;
- Not use genital piercing jewelry or other vaginal products, except menstrual absorption products.

During the trial, the female participant was asked to attend all scheduled trial visits whereas the male partner was only required to attend the screening visit. Each couple was asked to use 8 female condoms in total—4 while the ring was inserted and 4 without the ring. Each couple needed to complete a condom log at home to capture data on condom function and safety after each condom use. After using 4 female condoms in each of the trial periods, the female partner returned to be interviewed about the couple's experiences with condom and ring use. Interviewer-assisted questionnaires were used to gather acceptability data.

Study Products

The 2 trial products are described in Figure 1.

Ethical Considerations

The trial was approved by the institutional review boards of the California Family Health Council Inc, now known as Essential Access Health. The trial is registered with clinicaltrials.gov (NCT01755754). After reading and signing the informed consent and qualifying for study inclusion, couples were enrolled in the trial. Participants in the trial were reimbursed for time and travel expenses.

Randomization

Based on a predetermined randomization schedule, eligible couples were stratified according to the female partner's self-reported previous experience with female condoms. If the female partner had used 4 or more female condoms before participating in the trial, the couple was randomized within the "experienced" stratum in which the couples were randomized in a 1:1 ratio to sequence A or B. If the female partner had used fewer than 4 female condoms, the couple was randomized within the "less experienced" stratum in which the couples were randomized in a 1:1 ratio to sequence C or D. A statistical programmer (not involved in this trial) developed the random allocation sequence, using a validated statistical program in SAS Software.[15]

Sample Size and Statistical Methods

The hypothesis for the primary endpoints, total clinical failure, and its component failure events, was that function of the female condom with the silicone ring inserted was "noninferior" to FC2 without the silicone ring inserted regarding the rate of events within a margin of 8.0%; that is, the upper limit of the 2-sided 95% confidence interval (CI) for the difference in the occurrence of events (FC2 with ring—FC2 without ring) had to be below 8.0%.

Assuming a total clinical failure rate of 20% for the female condom (when used with or without the placebo vaginal ring),[13] and an intracouple correlation of 0.15, 66 couples using 4 female condoms during each trial period (264 uses in both the presence and absence of the placebo vaginal ring) would provide approximately 80% power (alpha equal to 0.05) to conclude noninferiority with an 8.0% margin. To allow for up to a 20% early discontinuation rate, enrollment of 80 couples was planned.

The main analysis for primary and secondary endpoints was according to the assigned condom use sequence among participants who provided relevant follow-up data on at least one sexual encounter *(completed act of vaginal intercourse)* using a female study condom with/without the placebo

FIGURE 1. Description of trial products. full color online

vaginal ring. The statisticians were blinded to the study arms until the database was locked.

RESULTS

Recruitment and Baseline

Eighty-one couples were enrolled (40 and 41 couples respectively per research center). In total, 79 couples completed the trial with each couple using at least one condom in each of the 2 periods. These couples comprise the main analysis population. The flowchart, overall and by research center, is shown in Figure 2. Two couples discontinued early; one couple did not adhere to the visit schedule and one couple was discontinued early because the female partner could not wear the vaginal ring. Twenty-five couples in this study participated in the "companion" study which evaluated the performance of male condoms when used with or without a silicone placebo vaginal ring. The results of this companion trial are presented in this journal edition.

Demographic characteristics are summarized in Table 1. The overall mean age across the 2 genders was 29.6 years and ranged from 19 to 50 years. The mean age for female participants in the trial was 28.8 years and for male participants 30.4 years. Participants were generally well educated with most male and female participants reporting post-high school experience with 40.8% overall completing a first degree or higher, whereas overall an additional 15.4% were students. A small difference was noted in educational attainment between male and female participants with more women (10%, n = 7) reaching at least college level compared with men. Few (9.3%) participants were unemployed.

Few women (35.8%, n = 29) had experience with the female condom before the trial with 64.2% having never used and another 14.8% (n = 12) only ever using female condoms 1–3 times. Only one woman had used them more than 10 times. Fewer men (23.4%, n = 19) had ever used the female condom compared with women.

Condom Use and Functionality of Condoms

In total, 596 female condoms were used in this trial by women in the main analysis population, 297 and 299 in the presence and absence of a placebo vaginal ring, respectively. Total female condom clinical failure in the presence of a vaginal ring was 14.1% with one failure event reported for 288 condoms and 2 failure events for 9 condoms. Total female condom clinical failure in the absence of a vaginal ring was 16.3% with one failure event reported for 284 condoms and 2 failure events in 16 condoms (Table 2).

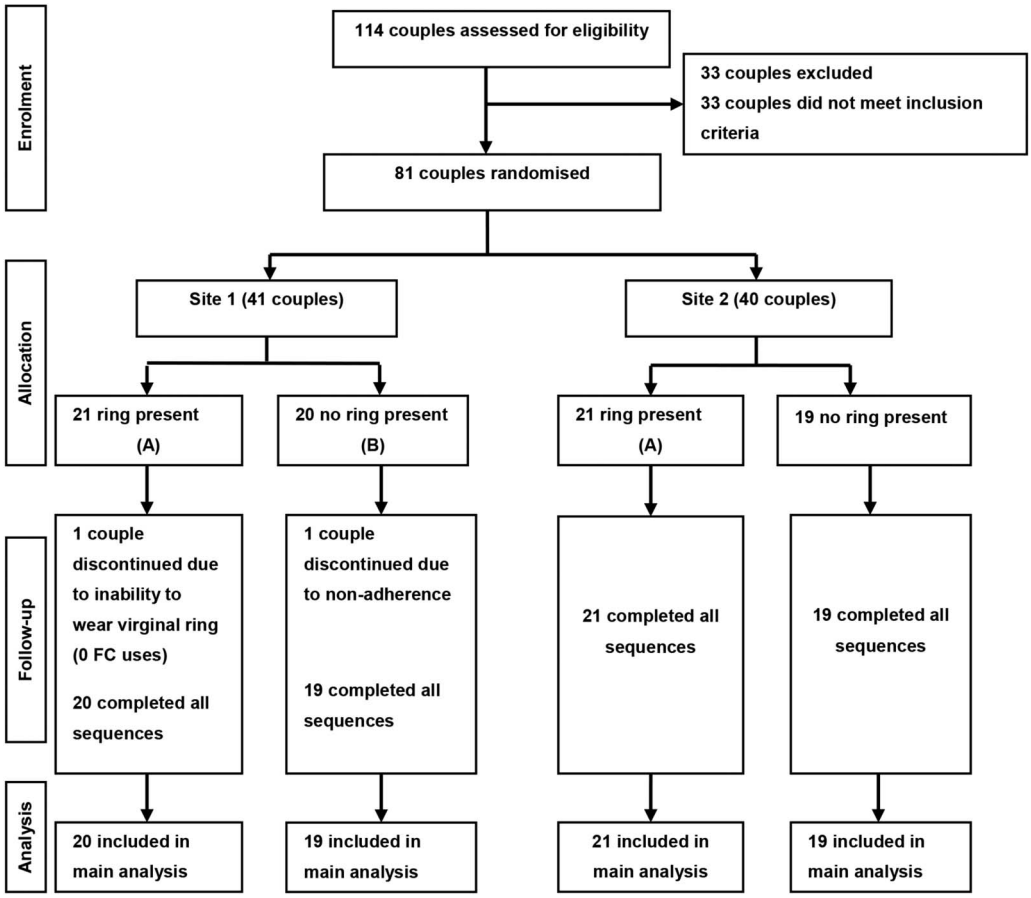

FIGURE 2. CONSORT flowchart.

TABLE 1. Demographics and Baseline Characteristics—Safety Population

	Participants		
	Females (N = 81)	Males (N = 81)	Overall (N = 162)
Demographic Characteristic	**n (%)**	**n (%)**	**n (%)**
Race:			
White	34 (42.0%)	22 (27.2%)	56 (34.6%)
Hispanic/Latino	18 (22.2%)	25 (30.9%)	43 (26.5%)
African American	16 (19.8%)	14 (17.3%)	30 (18.5%)
Asian or Pacific Islander	5 (6.2%)	3 (3.7%)	8 (4.9%)
Other	8 (9.9%)	17 (21.0%)	25 (15.4%)
Age (yr): Mean			
SD	28.8 (5.65)	30.4 (6.80)	29.6 (6.23)
Range	19–43	19–50	19–50
Highest level of education:			
Some high school	1 (1.2%)	3 (3.7%)	4 (2.5%)
High school diploma or equivalent	7 (8.6%)	14 (17.3%)	21 (13.0%)
Some college	35 (43.2%)	36 (44.4%)	71 (43.8%)
BA (Bachelor's degree)	26 (32.1%)	18 (22.2%)	44 (27.2%)
Post-graduate degree	12 (14.8%)	10 (12.3%)	22 (13.6%)
Employment status:			
Full-time	32 (39.5%)	43 (53.1%)	75 (46.3%)
Part-time	20 (24.7%)	16 (19.8%)	36 (22.2%)
Student	15 (18.5%)	10 (12.3%)	25 (15.4%)
Unemployed	4 (4.9%)	11 (13.6%)	15 (9.3%)
Homemaker	8 (9.9%)	0	8 (4.9%)
Disabled/unable to work	2 (2.5%)	1 (1.2%)	3 (1.9%)

Noninferiority was demonstrated for condom use with the ring, compared with that without the ring for all female condom failure modes. The difference between the total clinical failure probability (when used with the ring) and the total clinical failure probability (when used without the ring), calculated using a generalized estimating equation procedure, was −2.1% (95% CI: −7.8% to 3.6%). Because the upper bound of the CI of 3.6% was less than 8.0%, the null hypothesis, which stated that the total clinical failure rate differed by at least 8.0%, was rejected.

There was no report of vaginal ring expulsion during intercourse. There were 2 reports of vaginal ring removal where participants removed the vaginal ring after use of all 4 condoms. There was one event of a missing ring where the participant reported it had been present during all acts of intercourse as confirmed by feeling the ring before and after intercourse; however, the ring was not in place at the crossover visit. There was one additional nonclinical breakage after removal of the condom in the absence of the vaginal ring, which was not verified at the time of data collection and has not been included in the failure calculation.

Acceptability

For both genders, 82.3% participants felt that the placebo vaginal ring did not change the way in which they had intercourse (Table 3). However, some participants did change the way of inserting the female condom because of the vaginal ring. One male participant reportedly placed the female condom on his penis first, after previous discomfort was experienced by his female partner, and slid the female condom ring back. One female reportedly "inserted the female condom at an angle," one female participant reported that they were "more careful that the female condom was not dislodged or displaced," and one female participant reported that they "pushed the condom all the way down the penis shaft before inserting it."

Just under half of participants found that using the female condoms in combination with the vaginal ring was physically uncomfortable (female participants: 36/79; 45.6% and male participants: 37/79; 46.8%). In comparison, 32.9% (26/79) female participants and 27.8% (22/79) male participants found that using the female condom was uncomfortable even when the vaginal ring was not used.

Over a third of both female and male participants reported unsatisfactory sexual intercourse while using the female condom with or without the vaginal ring: 39.2% (31/79) female participants and 35.4% (28/79) male participants with vaginal ring use, and 36.7% (29/79) female participants and 36.7% (29/79) male participants without vaginal ring use.

Overall, the occurrence of treatment-emergent AEs (TEAEs) was low. Five TEAEs were reported during the trial in 4 female participants and one male participant: vulvovaginal discomfort (reported by 2 female participants), pelvic discomfort (reported by one female participant), bacterial vaginitis (reported by one female participant), and a genital burning sensation (reported by one male participant). Except for the event of bacterial vaginitis, all TEAEs were self-reported events that arose during female condom or female condom/ring use and that lasted more than one hour. All events resolved without sequelae. No serious AEs were reported.

DISCUSSION

Use of the female condom together with a placebo silicone vaginal ring did not result in increased condom failure rates, as shown by the noninferiority demonstrated for all modes of condom clinical failure when used with the ring, compared with use without the ring. The total clinical failure, total female condom failure and component failure rates reported are consistent with findings from earlier, similarly conducted studies.[16–17]

Almost half of women (45.6%) and men (46.8%) reported discomfort when using the female condom with the ring inserted. However, without the ring, a third of women (32.9%) and 27.8% men also reported discomfort. The high levels of discomfort experienced when the condom was used with the vaginal ring may be the result of poor fitting of the female condom. In this trial, a trained study investigator fitted the vaginal ring; however, the women were responsible for the female condom insertion. Although women were trained on correct insertion of the female condom, there may have been concerns regarding placement of the internal ring of the female condom and

TABLE 2. Female Condom Functionality

Condom Function	Condom Series	Condoms n	Mean Failure n = 79, n (%)	Difference	95% CI
Nonclinical breakage*	With ring	297	0	—	—
	Without ring	300	1 (0.3%)	—	—
Clinical slippage rate	With ring	297	0	—	—
	Without ring	299	1 (0.3%)	—	—
Clinical breakage rate	With ring	297	0	—	—
	Without ring	299	1 (0.3%)	—	—
Misdirection rate	With ring	297	13 (4.4%)	−1.4	−4.3 to 1.4
	Without ring	299	17 (5.7%)	—	—
Invagination rate	With ring	297	37 (12.5%)	−2.2	−7.9 to 3.6
	Without ring	299	43 (14.4%)	—	—
Total clinical failure rate	With ring	297	42 (14.1%)	−2.1	−7.8 to 3.6
	Without ring	299	47 (15.7%)	—	—
Total female condom failure†	With ring	297‡	42 (14.1%)	—	—
	Without ring	300§	49 (16.3%)	—	—

*Did not test for differences in nonclinical breakage as the same condom type was used in each period of the trial.

†Did not test for differences in total female condom failure as non-clinical breakage was not a contributing factor to female condom failure, because the same condom type was used in each period of the trial.

‡One failure event was reported for 288 condom uses, 2 failure events occurred in 9 condom uses.

§One failure event was reported for 284 condom uses, 2 failure events occurred in 16 condom uses.

possible dislodging of the vaginal ring, and consequently some women may have failed to push the female condom deeply enough into the vagina. Only a third of women and a quarter of men had experience with the female condom before the trial. Of those that had ever used female condoms, few had used it more than 3 times. This low level of female condom experience may have contributed to feelings of discomfort in using both with and without the placebo vaginal ring. It has been reported that female condom failures and user discomfort issues are reduced with practice.[18,19] In addition, vaginal ring acceptability increases over time.[20]

TABLE 3. Female Condom Acceptability Endpoints, With and Without the Vaginal Ring

	With Ring (N = 79)		Without Ring (N = 79)	
	Response	n (%)	Response	n (%)
Females				
Ring changed the way you had sex in any way	No	65 (82.3%)	—	—
	Yes	13 (16.5%)	—	—
Changed the way of inserting the female condom	No	75 (94.9%)	—	—
	Yes	3 (3.8%)	—	—
Physical comfort of female condoms during sex	Discomfort	36 (45.6%)	Discomfort	26 (32.9%)
	Neutral	22 (27.8%)	Neutral	32 (40.5%)
	Comfortable	20 (25.3%)	Comfortable	21 (26.6%)
General sense of sexual pleasure or satisfaction during sex	Dissatisfied	31 (39.2%)	Dissatisfied	29 (36.8%)
	Neutral	33 (41.8%)	Neutral	29 (36.7%)
	Satisfied	14 (17.7%)	Satisfied	21 (26. %6)
Males				
Ring changed the way you had sex in any way	No	65 (82.3%)	—	—
	Yes	13 (16.5%)	—	—
Changed the way of inserting the female condom	No	77 (97.5%)	—	—
	Yes	1 (1.3%)	—	—
Physical comfort of female condoms during sex	Discomfort	37 (46.9%)	Discomfort	22 (27.8)
	Neutral	24 (30.4%)	Neutral	38 (48.1)
	Comfortable	17 (21.5%)	Comfortable	19 (24.1)
General sense of sexual pleasure or satisfaction during sex	Dissatisfied	28 (35.4%)	Dissatisfied	29 (36.7)
	Neutral	33 (41.8%)	Neutral	30 (38.0)
	Satisfied	17 (21.5%)	Satisfied	20 (25.4)

A comprehensive review of vaginal ring acceptability reported that between 70% and 90% of users and 48%–97% of partners felt the ring during sex.[20] Our study data showed a lower proportion of women (n = 29, 36.7%) feeling the vaginal ring, whereas just under half (48.1%) of men felt the vaginal placebo ring, this is in line with other reported studies.[20] The lower level of reporting in women may be because of the use of the female condom which also has a ring inserted in the vagina. The woman may have attributed "feeling a ring during sex" to the female condom ring; however, this was not explored in the study and women were not asked whether they felt the female condom ring when the vaginal ring was not in place.

Using the female condom in a different way to its recommended use may increase risk of failure. The FC2 female condom uses an internal ring as the insertion and internal retention feature; however, other female condoms use different methods. The Cupid female condom[21] uses a medical grade sponge and the "V" Women's condom (developed by PATH) uses a dissolving cap for insertion and foam shapes on the central part of the condom body and therefore there is no retention feature that would interfere with the vaginal ring.[21]

The rates of condom use (male and female) at last sex show a positive trend in many regions with some Latin American and European countries reporting rates among 15–24-year-olds of more than 80%, although lower increase of around 30% have been recorded in some African countries.[1] In particular, condom use at last higher-risk sex has increased over the past 3 decades in most countries across the world and is as high as 80%–90% in some countries.[22] Vaginal rings do not protect against STIs and pregnancy and if rings are introduced into a population with high rates of condom use at last high-risk sex, it would be crucial to support the use of both methods. The 2 methods combined could potentially increase protection from HIV if there is a condom failure. Even if only a small portion of couples use the female condom and vaginal ring together it would be crucial for providers to have evidence that the 2 products are compatible so they can counsel those who choose to use both products. This is particularly important for female condoms because they were not recommended for use in the phase I/II/III Dapivirine ring trials and therefore this study is the first to report on their concomitant use.

The DVR does not protect against STIs, and countries that have high HIV rates are often burdened with high concomitant STI rates. It would therefore be important to counsel potential DVR users on the need to protect themselves from STIs, in a similar way to current counselling strategies for pre-exposure prophylaxis against HIV.

Limitations

Key limitations for this trial were that participants and research staff could not be blinded (although allocation concealment was used to limit the potential impact), and it was based exclusively on self-reported measures of condom use. Importantly, only the FC2 Female Condom brand was evaluated and other brands with different inner retention features may result in different experiences with concomitant use of the vaginal ring. Few men and women had prior experience of the female condom and as only 4 condom and ring uses were evaluated, participants may have required more experience to overcome some user challenges such as discomfort.

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