HHS Public Access

Predictors of Adherent Use of Diaphragms and Microbicide Gel in a Four-Arm, Randomized Pilot Study Among Female Sex Workers in Madagascar

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Abstract

Background—Participants' protocol adherence may influence assessments of the effectiveness of new female-controlled methods for sexually transmitted infection prevention.

Methods—In 2005 we conducted a randomized pilot study among female sex workers (FSWs) in Madagascar in preparation for sexually transmitted infection prevention trial of diaphragms and a vaginal microbicide. Participants (n = 192) were randomized into 4 arms: diaphragm plus microbicide (Acidform), diaphragm plus placebo gel hydroxyethyl cellulose (HEC), Acidform alone, or HEC alone. FSWs were seen weekly for 4 weeks. Using multivariable regression with generalized estimating equations, we assessed predictors of adherent product use during all sex acts in the last week. We collapsed the gel-diaphragm arms together and the gel-only arms together for this analysis.

Results—Between 43% and 67% of gel-diaphragm users (varying by visit) reported using study products during all sex acts in the last week, compared with 20% to 45% of gel-only users. Adherence increased with follow-up [visit 4 vs. visit 1 risk ratio (RR) for gel-diaphragm users: 1.55, $P<0.01$; for gel-only users, RR: 1.58, $P = 0.01$]. Gel-diaphragm users whose casual partners were never aware of products (RR: 2.02, $P = 0.03$) and who had experienced partner violence after requesting condom use (RR: 1.45, $P<0.01$) were more adherent. Gel-only users reporting lower

sexual frequency (1–9 weekly acts vs. ≥19 acts, RR: 1.98, $P<0.01$) and no sex with primary partners in the past week (RR: 1.54, $P=0.02$) were more adherent.

Conclusions—Gel-diaphragm users had better adherence than gel-only users, and predictors of adherence differed between groups. Addressing modifiable factors during counseling sessions may improve adherence.

Ftransmitted infections (stis) are those that do not rely (or rely emale-controlledmethods for prevention of hiv and sexually less) on cooperation from male partners. New female-controlled methods, including vaginal microbicides that could kill or deactivate sexually transmitted pathogens, are currently under development. Cervical barriers such as diaphragms, which were originally developed for contraception, are also being reconsidered for their ability to prevent disease.[1]

As with male condoms, effective protection using female-controlled methods is dependent on adherence. Recent research (largely short-term pilot studies) has found that adherence in microbicide and diaphragm studies was associated with the acceptability of product characteristics and instructions for use,[2,3,4,5] understanding of study concepts,[3,6] education,[7] and partner approval.[3–5,8–10] Knowledge about factors associated with consistent product use can be incorporated into counseling messages to potentially improve adherence.

We conducted a 4-week, randomized pilot study in preparation for an upcoming large-scale randomized controlled trial that will examine the effectiveness of the diaphragm with candidate vaginal microbicide for prevention of gonococcal and chlamydial infection among female sex workers (FSWs) in Madagascar. A primary objective of this pilot was to identify factors associated with adherent study product use to aid in the development of appropriate protocols and counseling messages for the upcoming trial.

MATERIALS AND METHODS

Study methods are described in detail elsewhere.[11] The pilot trial took place in 2005 in 4 cities in Madagascar: Antan-anarivo, Antsiranana, Mahajanga, and Toamasina.

Recruitment and Screening

Recruitment occurred though a peer-outreach program.[12,13] Peer counselors approached women in community venues to invite them to the study clinic for formal screening. FSWs attending the same clinics for routine care were also invited to screen.

Eligibility criteria included having at least 4 different sex partners in the past month, using condoms in less than 100% of sex acts in the previous 2 weeks, age 15 to 55 years, not pregnant or planning pregnancy in the next 2 months, with no allergy to latex, and no physical abnormality making diaphragm use impossible.

At screening, women underwent pregnancy and urinary tract infection testing. Pregnant women and those with urinary tract infections were discontinued from screening.

Randomization

Eligible women (n = 192) were randomized to 4 groups (n = 48 in each arm): (1) vaginal microbicide Acidform (TOPCAD, Chicago, IL) used with a latex All-flex Arcing Spring Diaphragm (Ortho Ortho-McNeil Pharmaceutical, Inc., Titusville, NJ); (2) inert control hydroxy ethylcellulose (HEC) placebo gel (ReProtect LLC, Baltimore, MD) used with a latex diaphragm; (3) HEC alone; and (4) Acidform alone. Randomization was stratified by site. Treatment assignments were partially masked (assignment of diaphragms was open, but neither staff nor participants was aware of gel assignments).

Protocols for Study Product Use

Women in the gel-diaphragm arms were instructed to use the diaphragm continuously, removing it once daily for cleaning. After cleaning, women used a study-provided applicator to dispense their assigned gel into the dome of the diaphragm, then immediately reinserted the diaphragm with gel. Participants in gel-only arms were instructed to insert their assigned gel intravaginally before each sex act, again using a study applicator.

All women were instructed to use male condoms with every act. Women returned all unused experimental products at the end of the study.

Enrollment and Follow-Up

At enrollment, participants received face-to-face interviews and counseling on use of condoms, diaphragms and/or gel, as appropriate for each study arm. All women received a pelvic exam and those randomized to use the diaphragm were fitted. Participants were given as many condoms as they wanted.

Follow-up visits occurred once weekly for 4 weeks. At each visit, women were interviewed about their sexual behavior and study product used. They underwent pelvic examination and received resupplies of assigned study products and condoms.

We compensated women $3.50 to 6.00 USD, depending on the visit, for their travel and time spent at the clinic.

Statistical Analysis

All analyses were conducted using SAS (SAS Institute, Version 9.1.3, Cary, NC).

For 2 reasons, for this analysis we collapsed the Acid-form-diaphragm and the HEC-diaphragm randomization arms into a single group ("gel-diaphragm users") and the HEC-alone and Acidform-alone arms into 1 group ("gel-only users"). First, given the nature of the products and instructions for use, we hypothesized that adherence was more likely to vary by arm type than by individual study arm. Second, because of the small sample size, we wanted to increase our power to detect associations between various predictors and adherent product use. Because adherence could also vary by individual arm, we controlled for randomization arm in all models.

Adherence was defined dichotomously: self-reported use of assigned products (gel with diaphragm for the 2 gel-diaphragm arms, and gel for the 2 gel-only arms) during 100% of

vaginal sex acts with all partners (husband, boyfriend(s), or casual partners) in the previous week, versus use of products at less than 100% of acts. We did not account for condoms in our adherence definition because condom use has been assessed elsewhere (Pettifor AE et al, unpublished data).[11] Person-time during which women reported no sex was excluded from this analysis.

Regression Models—We used regression models with generalized estimating equations[14,15] to assess the 1 week "risk" of adherent product use for women according to several predictors. We accounted for clustering resulting from repeated measurements on individual women and we specified the exchangeable working correlation matrix for all generalized estimating equations models.

Because of small sample size, we used Poisson regression with robust variance estimation[16,17] rather than log-binomial regression[18,19] to compute parameter estimates. We considered associations between adherent product use and several domains of participant characteristics: trial factors, demographic factors, reproductive factors, sexual behavior, product characteristics, and control/power issues.

Because we could achieve satisfactory model convergence with a limited number of predictor variables,[20] and to reduce the probability of missing important confounding effects apparent only in the presence of other factors,[21] we divided predictor variables by domain into 3 preliminary multivariable models (similar to Ingram et al.[22]): (1) trial and demographic factors; (2) reproductive and sexual behavior; and (3) product-related and control/power factors. Each preliminary model contained all variables specific to that domain.

We then conducted a manual backward elimination procedure with each domain-specific preliminary model to achieve the most parsimonious model, dropping variables one by one until all remaining predictors had Wald P values less than $a = 0.25$.[23]

With all variables surviving the backward elimination process of the domain-specific models, we constructed a single combined model. We then conducted another backward elimination procedure, removing variables one at a time until all remaining predictors had Wald test P values less than $a = 0.05$.

We conducted the preliminary and full model procedures separately for gel-diaphragm and gel-only users. The final models predicting adherent product use contained all variables that were significant predictors following the backward elimination procedure for either arm type.

Because of additional a priori concerns about confounding, we included randomization arm, age, visit, and sexual frequency in the last week in all domain-specific preliminary models, and we retained these variables in the final multivariable models.

Ethical Approval

All women gave written informed consent for screening and again for enrollment. The pilot study received ethical approval from the Comité d'Ethique auprès du Ministère de la Santé

in Madagascar and the Institutional Review Boards at the University of North Carolina at Chapel Hill and the Centers for Disease Control and Prevention, United States.

RESULTS

Nearly all participants (n = 188, 98%) completed 4 weeks of follow-up. This analysis includes 93 gel-diaphragm users who contributed 364 person weeks (PWs) of follow-up time and 96 gel-only users who contributed 381 PWs. Eight PWs were excluded because women reported no sex during that time interval or because of incomplete data on product use.

Participant Characteristics

By design, women were evenly distributed at enrollment by randomization arm and site (Table 1). Participants had a median age of 29 years, with a median age at first sex of 17 years and a median level of schooling of 6 years. Over half (61% in gel-diaphragm arms; 55% in gel-only arms) did not have a primary partner (husband or boyfriend), and a substantial minority (43% in gel-diaphragm arms; 35% in gel-only arms) shared their bedrooms with at least 2 additional people. Women in gel-diaphragm arms reported a median of 8 different partners and 10 acts in a typical week, whereas those in the gel-only arms had a median of 6 different partners and 9 acts in a typical week. Condom use with primary partners was less common than with casual partners: of those with a primary partner, 8% in the gel-diaphragm arms and 14% in the gel-only arms reported always or almost always using condoms with the primary partner, whereas 42% in the gel-diaphragm arms and 53% in the gel-only arms reported always or almost always using condoms with casual partners (Table 1).

Adherent Product Use Over Follow-Up

At the first follow-up visit, 43% of women in gel-diaphragm arms used study products during all acts in the previous week; this value increased to 49% at the second follow-up visit, 63% at the third follow-up visit, and 67% at the final follow-up visit. Overall, women in gel-only arms had lower compliance: 28% of women in gel-only arms at the first follow-up visit, 20% at the second visit, 31% at the third visit, and 45% at the final visit reported adherent use of gel during all acts with all partners in the last week.

Preliminary Multivariable Models: Domain-Specific Associations With Adherent Product Use

Measures of effect in Table 2 are adjusted for all variables in that domain as well as randomization arm, participant age, study visit, and number of acts in the previous week (Table 2).

Gel-Diaphragm Arms—Women's adherent use of diaphragm with assigned gel increased with each additional follow-up visit (Model 1, Table 2). Participants reporting previous use of female condoms for HIV prevention [RR: 1.42, 95% confidence interval (CI): 1.12–1.80], not having sex with a husband or boyfriend in the previous week (RR: 1.35, 95% CI: 1.00–1.81) (Model 2, Table 2), who did not conceal product use from casual partners (RR: 4.42,

95% CI: 1.23–15.91), whose partners were never aware of product use (RR: 2.00, 95% CI: 1.03–3.88), and who had experienced past violence from a casual partner after a suggestion of condom use (RR: 1.43, 95% CI: 1.14–1.80) (Model 3, Table 2) had significantly higher adherence with diaphragm and gel use during sex in the past week. In addition, reporting that study products were somewhat or very easy to conceal from casual partners (RR: 3.17, 95% CI: 0.92–10.90) and having no problems with study products in the past week (RR: 1.48, 95% CI: 0.96–2.28) (Model 3, Table 2) suggested higher adherence, though these associations were not statistically significant.

Women randomized to use their diaphragm with Acid-form had significantly lower adherence than those using the diaphragm with HEC (RR: 0.68, 95% CI: 0.51–0.91) (Model 1, Table 2), and women reporting a past unwanted pregnancy also had lower adherence (RR: 0.73, 95% CI: 0.57–0.95) (Model 2, Table 2).

Gel-Only Arms—Adherence in the gel-only arms also improved significantly by the final follow-up visit (visit 4 vs. visit 1; RR: 1.66, 95% CI: 1.16–2.38) (Model 1, Table 2), but other significant predictors of adherence for the gel-only arms differed from factors identified for the gel-diaphragm arms. Women from Tamatave (RR: 1.63, 95% CI: 1.00–2.65) (Model 1, Table 2) and those reporting fewer weekly acts (1–9 acts vs. 19 or more acts; RR: 2.01, 95% CI: 1.25–3.23) (Model 2, Table 2) had higher compliance, as did women who reported no sex with a husband or boyfriend in the past week (RR: 1.73, 95% CI: 1.17–2.56) (Model 2, Table 2).

We observed a suggestion of higher adherence among women randomized to use Acidform-only versus those using HEC-only (RR: 1.35, 95% CI: 0.94–1.92), and among older women (35 years) compared to the youngest participants (16–24 years) (RR: 1.62, 95% CI: 0.94–2.81) (Model 1, Table 2), though these associations were not statistically significant.

Adherence was not associated in either group with education, site, socioeconomic factors, prior participation in an STI or pregnancy prevention study, or past use of birth control.

Final Multivariable Models

Gel-Diaphragm Arms—After final multivariable adjustment, the strongest significant predictor of consistent gel and diaphragm use in the previous week was reporting not concealing product use from casual partners (RR: 4.75, 95% CI: 1.33–16.96); women who reported that casual partners were never aware of product use (RR: 2.02, 95% CI: 1.07–3.80) were also more adherent (Table 3). Increased experience with study products (visit 4 vs. visit 1, RR: 1.55, 95% CI: 1.24–1.95) and a past experience of violence after a request for condom use (RR: 1.45, 95% CI: 1.17–1.80) remained significantly associated with increased adherence among gel-diaphragm users following final adjustment. Finding products easy to conceal from casual partners (RR: 3.32, 95% CI: 0.98–11.23) and reporting no sex with a husband or boyfriend in the past week (RR: 1.27, 95% CI: 0.98–1.65) were suggestive of higher adherence.

Users of Acidform with the diaphragm had significantly lower adherence than women randomized to use HEC with the diaphragm (RR: 0.77, 95% CI: 0.60–0.98), as did women who reported a past unwanted pregnancy (RR: 0.73, 95% CI: 0.57–0.93) (Table 3).

Gel-Only Arms—In gel-only arms, after final adjustment, higher adherence was also associated with more product experience (visit 4 vs. visit 1, RR: 1.58, 95% CI: 1.10–2.28). Women reporting fewer weekly acts (1–9 vs. 19 or more acts, RR: 1.98, 95% CI: 1.29–3.03) and no sex with a husband or boyfriend in the previous week (RR: 1.54, 95% CI: 1.07–2.22) were also more likely to report gel use during all acts in the previous week (Table 3). Two other factors were suggestive of increased adherence after final adjustment: randomization to Acidform rather than HEC (RR: 1.34, 95% CI: 0.94–1.91) and older age (36 years vs. 16–24 years; RR: 1.55, 95% CI: 0.97–2.48).

DISCUSSION

In this short pilot study of FSWs in Madagascar, adherent use of study products was substantially higher among women randomized to use gel with diaphragm than among women using gel-only. The gap in adherence by arm type was sustained during follow-up, though the proportion of women reporting adherent product use during all acts generally increased over time for both gel-diaphragm and gel-only users.

Reasons for the disparity in adherence by arm type may be related to the recommended protocols for use. Gel-diaphragm use was not coitally-dependent; rather, women applied gel into the dome of the diaphragm once daily, inserted it, and wore it continuously, whereas gel-only users were asked to apply gel intravaginally before every act. The increased volume of gel present in the vagina for gel-only users may have been less acceptable or may have resulted in fear of conflict with partners, discouraging consistent use. (We reported previously that partners of gel-only users had mentioned excessive lubrication and wetness in the previous week at 30% of follow-up visits).[11] Of note, ease of covert product use was not a significant predictor of adherence among gel-only users.

Participant and product characteristics associated with adherent use differed for women randomized to gel-diaphragm and gel-only arms. After adjustment, gel-diaphragm users who reported that their casual partners were never aware of product use were significantly more likely to use their products compliantly, suggesting that women who were comfortable with covert use were more likely to use their products. Reinforcing this finding, gel-diaphragm users who reported that covert use was easy also had increased adherence, though this association was of borderline statistical significance. Interestingly, those reporting not concealing products from casual partners (reported at only 7 visits) also had significantly higher adherence. Though making inferences from such a small subgroup is difficult, this suggests that women who can engage in open communication with partners may also have higher levels of compliance. In light of these results, counseling sessions for the upcoming trial will include more extensive discussion and training related to covert use at baseline and during booster counseling at follow-up visits. Women will also be told in counseling sessions that although many women are able to use the products successfully during sex without their partner's knowledge, others choose to tell their partners about the products and

are also able to use the products successfully. The finding that adherence increased over follow-up further suggests that more time dedicated to training in product use may improve participant compliance.

For gel-only users, associations between several predictors and adherent product use trended in the same direction as for gel-diaphragm users, but nearly all associations failed to achieve statistical significance. Longer duration of follow-up remained a significant predictor of adherent use of gel in the past week, and 2 other factors—reporting fewer acts and not having sex with a husband or boyfriend in the past week – were also significantly associated with use of gel during all acts. The relationship between number of acts and increased adherence is likely due in part to our definition of adherence. Women had to use their assigned products in 100% of acts to be considered adherent; the higher their number of acts, the more difficult it became to clear this threshold. For this reason, it is important that researchers adjust for the number of acts when measuring adherence. On the other hand, higher sexual frequency may also be 1 component of overall risky sexual behavior, and individuals with 1 risky behavior often have others. Not having sex with a husband or boyfriend in the previous week was also associated with higher adherence for both arm types (significantly for gel-only users, nonsignificantly for gel-diaphragm users). This fits with our observation that women seemed to use their products less compliantly with primary partners than with casual partners.

Randomization assignment was somewhat associated with adherence for both arm types, but in opposite directions. Among gel-diaphragm users, those randomized to use Acid-form had lower compliance than those using HEC, whereas among the gel-only groups, women randomized to use Acid-form had somewhat higher compliance than those using HEC. Interpretation of the differences in adherence by randomization arm is challenging because of the study's small sample size and short follow-up period; we unfortunately did not have sufficient power to explore adherence differences by individual randomization arm, though we did control for study arm in all multivariable analyses. One hypothesis is that continuous use led to greater discomfort with Acidform, because the diaphragm is placed over the cervix, holding the Acidform gel directly onto sensitive cervical tissue, whereas gel-only users were exposed to intravaginal Acidform use, with gel dispersed over a larger surface area but in lower concentration throughout the vagina. However, participant's self-reports in the trial do not bear this out (reports of discomfort were approximately equal among users of Acidform with the diaphragm and Acidform alone).[11] Whatever the reason, variation in adherence between arms in the planned trial would have substantial implications for intent-to-treat analyses, because differences in STI rates between randomization arms could be due to the effect of the experimental products or simply because of differences in adherence.

Limitations and Strengths

Two intentional design aspects of this small pilot study—small sample size and short follow-up time—were nevertheless limitations. For example, as indicated earlier, we did not have adequate power to examine adherence by individual randomization arm; we similarly lacked the ability to explore adherence by partner type. Other predictors of adherence might have emerged with a larger sample. Our multivariate analyses attempted to minimize this sample

size limitation by initially dividing variables into separate domains and assessing the individual and joint impact of each variable within these domains. This approach, however, could fail to detect confounding relationships across domains because some factors were dropped at the domain level and not taken forward to the combined model. The pattern of increased adherence with increased follow-up time may not persist past the short follow-up of this pilot. An additional limitation is that sexual behavior data, including measures used to calculate adherence, were self-reported and may suffer from recall or social desirability biases.

These limitations are offset by several strengths. First, no previous study has explored factors associated with adherence for a combination microbicide-diaphragm prevention package. Second, participants were randomized, reducing the likelihood of baseline imbalance in the distribution of characteristics that may be associated with adherence. Third, our analysis methods allowed proper computation of associations given repeated measurements on participants. Fourth, because FSW behavior has been documented to vary by partner type,[24] we collected predictor data separately for casual and regular partners. Finally, the FSWs in this study are a highly relevant population group: they are at extremely high STI risk, yet have reduced ability to negotiate condom use.

CONCLUSION

The goal of this analysis was to identify factors that could be used to maximize adherent use of experimental study products in an upcoming effectiveness trial. Some variables that we hypothesized might be associated with product use were not related to adherence, including education, socioeconomic status, and vaginal hygiene practices. However, several factors were associated with increased adherence and will be integrated into counseling scripts and trial protocols.

At least 16 candidate vaginal microbicides are currently in various stages of human testing. A recent clinical trial among women in Zimbabwe and South Africa indicated that a prevention package of the diaphragm, lubricant gel, and condoms was no more effective than condoms alone at preventing HIV or STI acquisition,[25,26] and differential adherence between the randomization arms may have masked a treatment effect.[25] Finding an effective female-controlled method is clearly an important research priority, and exploring which characteristics make women choose to use it may be just as important.

Acknowledgments

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TABLE 1

Participant Characteristics at Enrollment

	Arm Type						
	Gel-Diaphragm		Gel-Only		Total		
Characteristic	n = 93	%*	n = 96	(%)*	n = 189	(%)*	
Arm							
Diaphragm plus AcidformTM	45	(48)	—	—	45	(24)	
Diaphragm plus HEC	48	(52)	—	—	48	(25)	
Acidform alone	—	—	48	(50)	48	(25)	
HEC alone	—	—	48	(50)	48	(25)	
Site							
Mahajanga	23	(25)	24	(25)	47	(25)	
Tamatave	24	(26)	24	(25)	48	(25)	
Toamasina	22	(24)	24	(25)	46	(24)	
Antananarivo	24	(26)	24	(25)	48	(25)	
Have a husband or boyfriend							
Yes	36	(39)	43	(45)	79	(42)	
No	57	(61)	53	(55)	110	(58)	
Marital status							
Never married	42	(45)	43	(45)	85	(45)	
Cohabitation/married	11	(12)	11	(12)	22	(12)	
Divorced/separated/widowed	40	(43)	42	(44)	82	(43)	
Share bedroom with ≥ 2 people							
Yes	40	(43)	34	(35)	74	(39)	
No	53	(57)	62	(65)	115	(61)	
Frequency of internal vaginal cleaning							
More than once a day	82	(88)	83	(87)	165	(87)	
About once a day	7	(8)	11	(12)	18	(10)	
Less than once day	4	(4)	2	(2)	6	(3)	
Ever used any birth control method							

Characteristic	Arm Type				Total	
	Gel-Diaphragm		Gel-Only			
	n = 93	%*	n = 96	(%)*	n = 189	(%)*
Yes	86	(92)	87	(91)	173	(92)
No	7	(8)	9	(9)	16	(8)
Ever unwanted pregnancy						
Yes	41	(44)	56	(58)	97	(51)
No	52	(56)	40	(42)	92	(49)
Ever used female condoms for HIV prevention						
Yes	16	(17)	15	(16)	31	(16)
No	77	(83)	81	(84)	158	(84)
Typical condom use with husband/boyfriend						
Never/rarely	21	(23)	23	(24)	44	(23)
Sometimes	11	(12)	13	(14)	24	(13)
Always/almost always	3	(3)	6	(6)	9	(5)
No husband/boyfriend	57	(62)	53	(55)	110	(58)
Typical condom use with casual partners						
Never/rarely	12	(13)	4	(4)	16	(8)
Sometimes	42	(45)	41	(43)	83	(44)
Always/almost always	39	(42)	51	(53)	90	(48)
Ever refused sex if casual partner refused to use condom						
No	23	(25)	15	(16)	38	(20)
Yes	69	(74)	80	(83)	149	(79)
Any casual partner ever violent because asked to use condom						
No	79	(85)	70	(73)	149	(79)
Yes	14	(15)	26	(27)	40	(21)
Participated in previous trial of STI or pregnancy prevention product						
No	66	(71)	65	(68)	131	(69)
Yes	26	(28)	31	(32)	57	(30)
	Median	Range	Median	Range	Median	Range
Age, (yrs)	28	17–54	30	16–51	29	16–54

Characteristic	Arm Type					
	Gel-Diaphragm		Gel-Only		Total	
	n = 93	%[*]	n = 96	(%)[*]	n = 189	(%)[*]
Age at coital debut, yrs	17	12–28	17	13–20	17	12–28
Education, yrs	6	0–13	5.5	0–12	6	0–13
No. sex partners in typical week	8	3–60	6	2–40	7	2–60
No. sex acts in typical week	10	3–60	9	2–45	10	2–60

[*] Because of rounding and missing data, not all categories sum to 100%.

TABLE 2

Preliminary, Domain-Adjusted Models Predicting Self-Reported Adherent Use of Assigned Study Products

Characteristic	Arm Type								
	Gel-Diaphragm (n = 364 Visits) n and % Adherent				Gel-Only (n = 381 Visits) n and % Adherent				
	n	%	RR	95% CI	P	n	%	RR	95% CI	P
Model 1: Trial and demographic factors [*]										
Arm										
Diaphragm plus Acidform	78	45.1	0.68	0.51, 0.91	<0.01	—	—	—	—	
Diaphragm plus HEC (referent)	124	64.9	1.	—		—	—	—	—	
AcidformTM alone	—	—	—	—		69	36.5	1.35	0.94, 1.92	0.10
HEC alone (referent)	—	—	—	—		50	26.0	1.	—	
Visit										
Week 1 (referent)	39	43.3	1.	—		27	28.4	1.	—	
Week 2	45	48.9	1.15	0.92, 1.44	0.22	19	20.2	0.75	0.49, 1.13	0.17
Week 3	57	62.6	1.43	1.13, 1.82	<0.01	30	31.3	1.11	0.76, 1.64	0.59
Week 4	61	67.0	1.57	1.23, 1.99	<0.01	43	44.8	1.66	1.16, 2.38	<0.01
Site										
Mahajanga	49	54.4	0.93	0.64, 1.35	0.70	28	29.5	1.16	0.69, 1.94	0.58
Tamatave	49	51.6	0.90	0.61, 1.32	0.59	36	37.5	1.63	1.00, 2.65	0.05
Toamasina	45	54.2	1.00	0.60, 1.66	0.99	30	31.6	1.46	0.84, 2.55	0.18
Antananarivo (referent)	59	61.5	1.	—		25	26.3	1.	—	
Age										
16–24 yr (referent)	60	52.2	1.	—		23	24.5	1.	—	
25–30 yr	67	59.8	1.19	0.87, 1.63	0.27	36	36.0	1.38	0.79, 2.44	0.26
31–35 yr	19	43.2	0.83	0.50, 1.39	0.48	19	21.6	0.87	0.44, 1.70	0.68
36+ yrs	56	60.2	1.20	0.84, 1.71	0.31	41	41.4	1.62	0.94, 2.81	0.08
Education										
5 yr	107	58.8	1.16	0.83, 1.63	0.39	60	31.6	1.20	0.81, 1.77	0.37
>5 yr (referent)	95	52.2	1.	—		59	30.9	1.	—	
Share bedroom with 2 people										

		Arm Type								
	Gel-Diaphragm (n = 364 Visits) n and % Adherent					Gel-Only (n = 381 Visits) n and % Adherent				
Characteristic	n	%	RR	95% CI	P	n	%	RR	95% CI	P
Yes	96	60.8	1.15	0.86, 1.54	0.36	48	35.8	1.26	0.85, 1.86	0.25
No (referent)	106	51.5	1.	—		71	28.7	1.	—	
Participated in STI or pregnancy prevention study										
Yes (referent)	56	53.9	1.	—		37	30.1	1.	—	
No	145	56.6	0.96	0.72, 1.28	0.79	82	31.8	0.91	0.62, 1.33	0.62
Model 2: Sexual and reproductive factors[*]										
Ever unwanted pregnancy										
Yes	71	44.9	0.73	0.57, 0.95	0.02	74	33.3	1.00	0.69, 1.47	0.98
No (referent)	131	63.6	1.	—		45	28.3	1.	—	
No. sex acts in previous week										
1–9 acts	47	61.0	1.11	0.85, 1.45	0.46	40	40.8	2.01	1.25, 3.23	<0.01
10–18 acts	98	59.8	1.02	0.80, 1.31	0.88	59	31.9	1.32	0.90, 1.96	0.16
19 acts (referent)	57	46.3	1.	—		20	20.4	1.	—	
Baseline condom use with casual partners										
Never/rarely	30	62.5	1.24	0.88, 1.76	0.22	6	37.5	1.09	0.63, 1.49	0.63
Sometimes	93	57.4	1.06	0.82, 1.37	0.64	52	31.7	1.29	0.52, 3.17	0.58
Always/almost always (referent)	79	51.3	1.	—		61	30.4	1.	—	
Ever female condoms for HIV prevention										
Yes	47	73.4	1.42	1.12, 1.80	<0.01	22	36.7	1.45	0.94, 2.22	0.09
No (referent)	155	51.7	1.	—		97	30.2	1.	—	
Used any birth control method ever										
Yes	191	40.7	1.32	0.65, 2.68	0.43	112	32.4	1.84	0.77, 4.41	0.17
No (referent)	11	56.7	1.	—		7	20.0	1.	—	
Frequency of internal vaginal cleaning										
Once a day or less often	23	53.5	1.18	0.80, 1.74	0.40	18	35.3	1.18	0.69, 2.02	0.54
More than once a day (referent)	179	55.8	1.	—		101	30.6	1.	—	
Had sex with husband/boyfriend in last week										
No	162	61.1	1.35	1.00, 1.81	0.05	94	36.9	1.73	1.17, 2.56	<0.01

Characteristic	Arm Type									
	Gel-Diaphragm (n = 364 Visits) n and % Adherent					Gel-Only (n = 381 Visits) n and % Adherent				
	n	%	RR	95% CI	P	n	%	RR	95% CI	P
Yes (referent)	40	40.8	1.	—		25	19.8	1.	—	
Model 3: Product-related and power/control factors *										
Ease of concealing products from casual partners										
Very/somewhat easy	206	61.7	3.17	0.92, 10.90	0.07	105	35.7	1.62	0.90, 2.93	0.11
Did not conceal	7	43.8	4.42	1.23, 15.91	0.02	7	18.9	2.26	0.82, 6.25	0.12
Very/somewhat hard (referent)	2	14.3	1.	—		7	15.6	1.	—	
Importance of casual partners not knowing about products										
Very important	97	59.5	1.01	0.81, 1.25	0.96	98	34.8	1.55	0.71, 3.39	0.28
Moderately important	16	35.6	0.73	0.52, 1.01	0.06	10	25.0	1.17	0.59, 2.30	0.65
Not important (referent)	87	58.0	1.	—		11	20.8	1.	—	
How often casual partners aware of product use?										
Never	163	62.0	2.00	1.03, 3.88	0.04	93	35.0	1.79	0.66, 4.84	0.25
Sometimes	32	42.7	1.74	0.91, 3.33	0.09	22	28.2	2.00	0.75, 5.36	0.17
Always (referent)	6	31.6	1.	—		4	15.4	1.	—	
Experienced problems with products in previous week										
No	192	58.9	1.48	0.96, 2.28	0.07	110	32.9	1.21	0.60, 2.44	0.60
Yes (referent)	10	30.3	1.	—		9	22.0	1.	—	
How much control over condoms with casual partners										
None/a little bit	81	50.3	0.95	0.74, 1.21	0.68	49	34.3	1.28	0.90, 1.81	0.17
A lot/complete (referent)	121	59.6	1.	—		70	29.4	1.	—	
Any casual partner ever violent because asked to use condom										
Yes	44	78.6	1.43	1.14, 1.80	<0.01	36	35.3	1.14	0.80, 1.62	0.47
No (referent)	158	51.3	1.	—		83	29.8	1.	—	

*
Each model adjusts for all domain-specific variables; presented estimates controls for all other variables in that domain. All models are also adjusted for randomization arm, age, study visit and number of sex acts in previous week.

TABLE 3

Multivariable Regression of Adherent Use of Assigned Study Products

| | Arm Type | | | |
| | Gel-Diaphragm | | Gel-Only | |
Characteristic	RR	95% CI	RR	95% CI
Arm				
Diaphragm plus Acidform	0.77	0.60, 0.98	—	—
Diaphragm plus HEC (referent)	1.	—	—	—
AcidformTM alone	—	—	1.34	0.94, 1.91
HEC alone (referent)	—	—	1.	—
Study visit				
Visit 1 (referent)	1.	—	1.	—
Visit 2	1.19	0.96, 1.47	0.78	0.52, 1.17
Visit 3	1.45	1.15, 1.82	1.06	0.71. 1.59
Visit 4	1.55	1.24, 1.95	1.58	1.10, 2.28
Age				
16–24 yrs (referent)	1.	—	1.	—
25–30 yrs	1.16	0.87, 1.52	1.45	0.85, 2.47
31–35 yrs	0.88	0.54, 1.41	0.95	0.50, 1.80
36+ yrs	1.09	0.80, 1.51	1.55	0.97, 2.48
No. sex acts in previous week				
1–9 acts	1.16	0.90, 1.49	1.98	1.29, 3.03
10–18 acts	1.04	0.82, 1.32	1.34	0.92, 1.97
19 acts (referent)	1.	—	1.	—
Ever unwanted pregnancy				
Yes	0.73	0.57, 0.93	1.02	0.71, 1.48
No (referent)	1.	—	1.	—
Ease of concealing products from casual partners				
Very/somewhat easy	3.32	0.98, 11.23	1.58	0.84, 3.00
Did not conceal	4.75	1.33, 16.96	1.55	0.61, 3.98
Very/somewhat hard (referent)	1.	—	1.	—
Casual partners aware of product use				
Never	2.02	1.07, 3.80	1.69	0.56, 5.13
Sometimes	1.67	0.89, 3.15	1.73	0.57, 5.18
Always (referent)	1.	—	1.	—
Sex with a husband or boyfriend in past week				
Yes (referent)	1.	—	1.	—
No	1.27	0.98, 1.65	1.54	1.07, 2.22
Any casual partner ever violent because ask to use condom				
Yes	1.45	1.17, 1.80	1.17	0.83, 1.63
No (referent)	1.	—	1.	—