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Authors

Sawaya, GF
Chirenje, MZ
Magure, MT
et al.

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Effect of Diaphragm and Lubricant Gel Provision on Human Papillomavirus Infection Among Women Provided With Condoms

A Randomized Controlled Trial

George F. Sawaya, MD, Mike Zvavahera Chirenje, MD, Mildred Tsitsi Magure, MD, Jennifer L. Tuveson, Yifei Ma, Stephen C. Shiboski, PhD, Maria M. Da Costa, Joel M. Palefsky, MD, Anna-Barbara Moscicki, MD, Rudo Makunike Mutasa, MD, Tsungai Chipato, MD, and Karen K. Smith-McCune, MD, PhD

OBJECTIVE: To estimate the effect of providing women with a latex diaphragm, lubricant gel, and male condoms (intervention) compared with condoms alone (control) on human papillomavirus (HPV) incidence and clearance.

METHODS: Participants were 2,040 human immunodeficiency virus (HIV)–negative Zimbabwean women enrolled in a randomized trial estimating the effect of the intervention on HIV acquisition. Clinicians collected cervical samples for HPV testing at baseline, 12 months, and exit. L1 consensus polymerase chain reaction primers were used to determine HPV presence and type.

RESULTS: We found no differences in the following outcomes: HPV prevalence at the time of the first postenrollment HPV test (intention-to-treat analysis, relative risk [RR] 1.02, 95% confidence interval [CI] 0.90–1.16); HPV incidence at 12 months among women HPV-negative at baseline (RR 0.95, 95% CI 0.80–1.14); and HPV clearance at 12 months among women HPV-positive at baseline (RR 0.80, 95% CI 0.61–1.05). Clearance of HPV type 58 was lower in the intervention group at 12 months (RR 0.67, 95% CI 0.48–0.92), but not at exit (RR 0.93, 95% CI 0.75–1.16); clearance of HPV type 18 was lower in the intervention group at exit (RR 0.55, 95% CI 0.33–0.89), but not at 12 months (RR 0.55, 95% CI 0.29–1.05). Women reporting diaphragm/gel use at 100% of prior sex acts had a lower likelihood of having one or more new HPV types detected at 12 months (RR 0.75, 95% CI 0.58–0.96) and exit (RR 0.77, 95% CI 0.59–0.99).

CONCLUSION: Among women receiving risk reduction counseling and condoms in an HIV prevention program, diaphragm plus lubricant gel provision did not affect HPV incidence or clearance.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00211459

(Obstet Gynecol 2008;112:990–7)

LEVEL OF EVIDENCE: I

Human papillomavirus (HPV) is widely considered to be the causative agent of cervical cancer,[1] a disease diagnosed in nearly 500,000 women annually worldwide.[2] Although vaccines targeting the most virulent oncogenic HPV types hold great promise,[3] current vaccines are expensive. Sustainable and affordable strategies to con-

From the Departments of Obstetrics, Gynecology and Reproductive Sciences and Epidemiology and Biostatistics, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California; Women's Global Health Imperative, Department of Obstetrics and Gynecology, University of Zimbabwe–University of California, San Francisco Research Programme on Women's Health, Harare, Zimbabwe; Departments of Pediatrics and Medicine, University of California, San Francisco, San Francisco, California.

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Corresponding author: George F. Sawaya, MD, 3333 California Street, San Francisco, CA 94118; e-mail: sawayag@obgyn.ucsf.edu.

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trol spread of HPV, especially in low-resource settings, are of major public health importance.

Multiple observational studies demonstrate consistent associations between barrier contraceptive use (both condoms and diaphragms) and decreased risk of HPV infection[4,5] and cervical neoplasia.[6–15] The U.S. Preventive Services Task Force summarized evidence on primary prevention of cervical cancer and reported that diaphragm use alone was associated with a 30–80% decreased likelihood of cervical cancer.[16] Although a randomized trial of condoms demonstrated efficacy for both regression of precancerous cervical lesions and HPV infections,[17] no randomized trials have been performed to determine the effect of diaphragm use on HPV infection or cervical neoplasia. We estimated the effect of provision of a latex diaphragm, lubricant gel, and male condoms (intervention) compared with condoms alone (control) on incidence and clearance of HPV infection in the setting of a randomized trial.

MATERIALS AND METHODS

Participants were sexually active HIV-negative women enrolled in a multicentered (Zimbabwe and South Africa), open-label, randomized trial estimating the effect of providing a latex diaphragm with a lubricant gel along with male condoms compared with male condom provision alone on HIV seroincidence; details and results of this trial, the Methods for Improving Reproductive Health in Africa (MIRA) study (ClinicalTrials.gov number NCT00211459), are presented elsewhere.[18]

The study reported here was conducted only at the Zimbabwe site at two clinics: Chitungwiza, a periurban municipality near Harare; and Epworth, a poorer and less developed suburb of Harare. Women were recruited from September 2003 to September 2005. Beginning February 2004, enrollment in the HPV study was offered to main trial enrollees; 2,040 of 2,089 (97.6%) women accepted and gave written informed consent. As per the main study protocol, all women were counseled about and provided male condoms at trial entry and at each visit. Counseling included information on the importance of condom use at all sex acts in the prevention of HIV.

Randomly permuted blocks of sizes 8, 10, and 12 were used for the randomization scheme. At the point of randomization, a sealed, opaque envelope containing the randomization assignment was retrieved by study staff and opened by the participant. Those assigned to the intervention group received a clinician-fitted latex diaphragm (Ortho-McNeil Pharmaceutical, Raritan, NJ), a supply of lubricant gel (Replens, Lil' Drug Store Products, Cedar Rapids, IA), and a supply of male condoms; the control group received condoms alone.

The study protocol was reviewed and approved by the University of California, San Francisco Committee on Human Research and by the local ethics review committee, the Medical Research Council of Zimbabwe, and the Medicines Control Authority of Zimbabwe.

At the baseline visit, all women underwent a speculum examination. Clinicians collected specimens for cervical cytology using a spatula and an endocervical brush. For HPV testing, a polyester swab was used to swab the cervix and endocervix under direct visualization; the swab was placed in specimen transport medium (Digene Diagnostics, Silver Spring, MD) and stored initially at 4°C for up to 4 days and subsequently at –20°C. Self-sampling was performed at 3-month intervals at the regularly scheduled clinic visits. Participants were instructed to place the swab into the vagina as far as it would comfortably go and twist the swab around its axis; the procedure was repeated with a second swab. Participants placed both swabs in transport medium. At the 12-month visit, clinicians performed an additional speculum examination to collect a cervical sample for HPV testing after the self-collected swab was obtained. At study exit, only a clinician-collected sample was obtained. At each visit, information about condom use and adherence to study products was determined by structured interview.

Samples were shipped monthly to University of California, San Francisco (Palefsky laboratory) for analysis using L1 consensus polymerase chain reaction primers and primers for amplification of the human β-globin gene. Thawed tubes were heated to 56°C for 1 hour to inactivate viruses and then digested overnight with proteinase K[19]; an aliquot was precipitated and concentrated. After 30 amplification cycles, 6 microliters of amplification mixture was applied to a nylon membrane and probed with a biotin-labeled HPV L1 consensus probe mixture. A separate membrane was probed with a biotin-labeled probe to the human β-globin gene. Specimens positive with the HPV consensus probe mixture were then assayed for the following 29 different HPV types: 6, 11, 16, 18, 26, 31, 32, 33, 35, 39, 40, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 66, 68, 69, 70, 73, a variant of 82, 83, and 84; the following 10 HPV types were included together in a probe mixture: 2, 13, 34, 42, 57, 62, 64, 67, 72, and 82 (known as "mixed" types). Specimens positive for the generic probe, but negative for the 39 specific types were considered to have an "untyped" sample.

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We defined oncogenic HPV as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

We anticipated that 2,200 women would enroll in Zimbabwean sites and that 10% would be lost to follow-up. Assuming an HPV prevalence ranging from 20% to 40% and an annual HPV incidence of 8%, we estimated that we would have 80% power to detect relative hazards of at least 0.63 for the high prevalence estimate and 0.74 for the low estimate, (two-tailed alpha=0.05). We considered reductions of this magnitude to be clinically important. The primary outcomes were based on results of clinician-collected HPV testing (up to three tests per participant). In an intention-to-treat analysis, we evaluated the effect of diaphragm/gel provision on prevalence of HPV at the time of the first postenrollment clinician-collected test. We focused on detection of any HPV type, any oncogenic HPV type, and the most common oncogenic HPV types in Zimbabwe (types 16, 18, 33, and 58, as determined by prevalence at baseline).

We defined HPV incidence in two ways: 1) detection of any "new" HPV type(s) (ie, one not detected at baseline) among all participants, and 2) detection of any HPV among women with no HPV detected at baseline. We estimated HPV incidence proportion at two predefined time points: 12 months and study exit. We estimated incidence of any oncogenic HPV and incidence of HPV types 16, 18, 33, and 58 using these two definitions. We defined a "12-month" test as one performed 11 to 16 months after the baseline HPV test; tests performed after 16 months (but within 2 weeks of study closure) were defined as "exit" tests.

We defined HPV clearance as nondetection of one or more HPV type(s) among women with any HPV detected at baseline. Samples that were untyped at baseline were not considered cleared if a specific HPV type was detected at follow-up. We estimated overall clearance of all oncogenic HPV types and type-specific clearance of HPV types 16, 18, 33, and 58, defined as nondetection of these types among women with one or more of these types detected at baseline. We estimated HPV clearance proportion at 12 months and study exit.

Using results from both self- and clinician-collected tests (up to nine tests per participant), we also used the Kaplan-Meier method to estimate the cumulative probability of HPV occurrence across the entire study period for each randomized group. We used a similar approach to estimate type-specific HPV clearance, defined as two subsequent consecutive tests negative for the HPV type detected at baseline and no future tests positive for that type.

We performed a "per-protocol" analysis by restricting our main analyses to women reporting diaphragm/gel use at 100% of prior sex acts. In sensitivity analyses, we expanded our definition of oncogenic HPV to include five additional HPV types (26, 53, 66, 73, and 82).[20] In intention-to-treat analyses, we excluded HPV tests with no detectable β-globin (n=99, or 4.9% of clinician-collected tests) and those performed more than 14 days after study exit (n=8); we also excluded women with no postenrollment HPV tests due either to lost to follow-up or study withdrawal (n=107). In all other analyses, we additionally excluded women with a missing baseline HPV test (n=5) and those with untyped HPV at both baseline and follow-up (n=16). We calculated relative risks and 95% confidence intervals for outcomes at discrete preestablished time points (time of first postenrollment test, at 12 months, and at study exit).

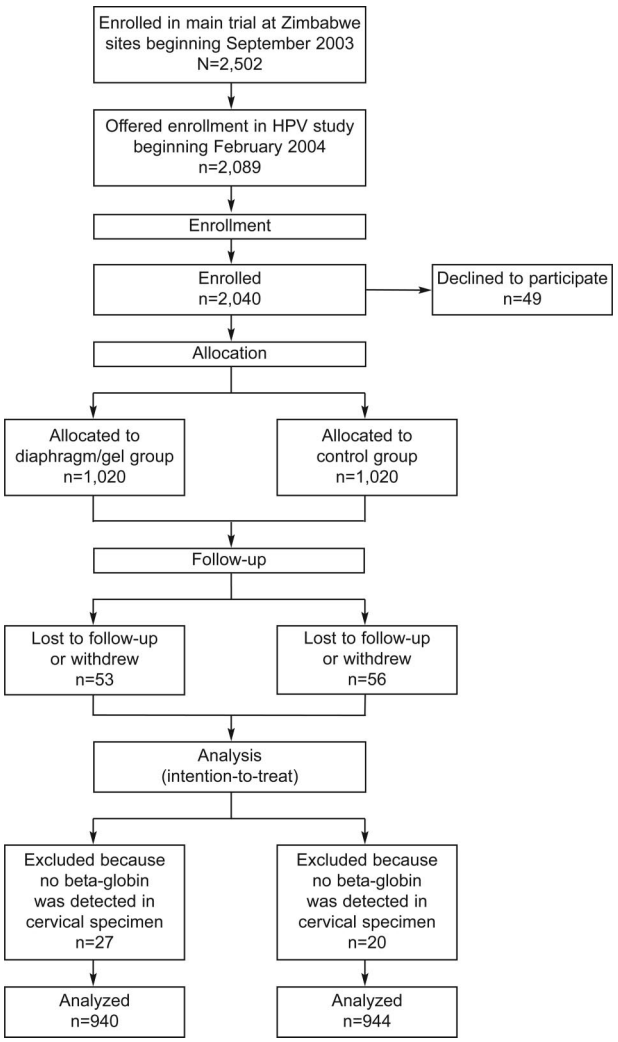

Fig. 1. Trial profile. HPV, human papillomavirus.
Sawaya. Effect of Diaphragm on HPV. Obstet Gynecol 2008.

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Table 1. Sociodemographic Characteristics, Reproductive History, and Sexual Behaviors at Baseline, by Group Assignment

	Group Assignment	
Category	Intervention (n=1,020)	Control (n=1,020)
Age (y)		
24 or younger	38.3	36.0
25–34	45.6	46.3
35 or older	16.1	17.8
At least high school education	47.7	48.5
Earned income in past year	75.5	73.6
Employed	27.1	24.0
Living together with regular partner	96.1	95.7
Religion (Christian vs other/none)	94.5	94.4
Lifetime sexual partners	1.3 (1–20)	1.4 (1–20)
Age at first sex (y)	18.7 (10–28)	18.6 (11–28)
Coital frequency per wk		
3 times or less	52.0	50.4
More than 3 times	48.0	49.6
Regular partner circumcised		
Yes	17.5	14.7
No	67.1	69.6
Don't know	15.4	15.7
Tested positive for one or more STD(s)*	6.4	7.4
Tested positive for HSV-2	49.7	51.9
High behavior risk: at least one indicator†	23.3	24.9
High partner risk: at least one indicator‡	66.1	65.8
Used condom at last sex	70.8	73.1
Frequency of condom use in past 3 mo		
Never	31.8	28.5
Sometimes	43.0	42.9
Always	25.2	28.5
Ever used diaphragm from screening questionnaire	0.10	0.20
Current contraceptive use from screening questionnaire		
Long term§	2.6	2.4
Injectable hormones	14.2	13.9
Pill‖	65.1	65.1
Barrier¶	10.2	11.5
Other/none	7.9	7.2
Currently smoking cigarettes	0	0.3
Has had 4 or more live births	18.0	19.2
Abnormal cytology at baseline (ASC-US or worse)	18.3	17.7
Human papillomavirus detected (any)	25.2	23.8
Human papillomavirus type 16	4.3	5.1
Human papillomavirus type 18	2.9	1.6
Human papillomavirus type 33	1.9	2.1
Human papillomavirus type 58	5.6	4.4
Condyloma present#	0.20	0.29

STD, sexually transmitted diseases; HSV, herpes simplex virus; ASC-US, atypical squamous cells of undetermined significance.
Data are % or mean (range).

* At least one positive test for *Chlamydia trachomatis*, *Neisseria gonorrhea*, *Trichomonas vaginalis*, or syphilis at screening or baseline.

† Indicators include any exchange of sex for money/food/drugs/shelter, two or more sexual partners within last 3 months, ever had vaginal sex under influence of drugs/alcohol in last 3 months, ever used needle for injectable drug use, ever had anal sex.

‡ Indicators include having any sexual partners test positive for human immunodeficiency virus, suspect or know that regular partner had other sex partners in the last 3 months, ever had vaginal sex when partner was under influence of drugs/alcohol in last 3 months, regular partner was away from home for 1 or more months.

§ Long-term methods include tubal ligation, vasectomy, intrauterine device, implants such as levonorgestrel 150 mg rods implant (Jadelle, Leiras Oy,Turku, Finland) and levonorgestrel 216 mg capsules implant (Norplant, Wyeth-Ayerst Laboratories, Philadelphia, PA).

‖ Pill methods include combined oral contraceptive and progesterone only pills.

¶ Barrier methods include male or female condoms.

Warts clinically observed on perineum, vulva, vaginal epithelium, or cervical epithelium.

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Table 2. Human Papillomavirus Prevalence at the Time of the First Postenrollment Clinician-Collected Test Among All Participants, Intention-to-Treat Analysis (N=1,884)*

Outcome	Group Assignment		Relative Risk (95% CI), Intervention vs Control
	Intervention (n=940)	Control (n=944)	
Prevalence of any HPV type	304 (32.3)	299 (31.7)	1.02 (0.90–1.16)
Prevalence of any oncogenic HPV type(s)	176 (18.7)	146 (15.5)	1.21 (0.99–1.48)
HPV type 16 prevalence	43 (4.6)	46 (4.9)	0.94 (0.63–1.41)
HPV type 18 prevalence	28 (3.0)	15 (1.6)	1.87 (1.01–3.49)
HPV type 33 prevalence	22 (2.3)	20 (2.1)	1.10 (0.61–2.01)
HPV type 58 prevalence	45 (4.8)	28 (3.0)	1.61 (1.02–2.56)

CI, confidence interval; HPV, human papillomavirus.
Data are n (%) unless otherwise specified.
Oncogenic HPV types defined as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.
* Excludes women with no postenrollment human papillomavirus test (n=109) and women with first postenrollment test negative for beta-globin (n=47).

Between-group differences in cumulative incidence and clearance probabilities were assessed using the log rank test.

The Bill and Melinda Gates Foundation funded and approved the HPV study but had no other role in data collection, analysis, data interpretation or reporting of results. All authors had access to the data and agreed with the results as submitted for publication.

RESULTS

Figure 1 describes the participants' progression through the phases of the trial. Characteristics of study participants were similar between groups at baseline (Table 1); the baseline prevalence of HPV type 18 was somewhat higher in the intervention group (P=.05). In an intention-to-treat analysis, HPV prevalence at the time of the first postenrollment clinician-collected test was the same in the two groups (Table 2). In the intervention group, prevalence of HPV types 18 and 58 was higher at the time of the first postenrollment HPV test.

Table 3 shows HPV incidence at 12 months by randomized group; no differences were demonstrable for any outcome. Results were similar at study exit (data not shown). Cumulative HPV incidence rates

Table 3. Human Papillomavirus Incidence at 12 Months Among All Participants and Among Those With No Human Papillomavirus Detected at Baseline

Populations and Outcomes at 12 Mo	Group Assignment		Relative Risk (95% CI), Intervention vs Control
	Intervention	Control	
All participants (n=1,534)*			
Group n	772	762	
One or more new HPV type(s) detected	176 (22.8)	182 (23.9)	0.95 (0.80–1.14)
One or more new oncogenic HPV type(s) detected	90 (11.7)	85 (11.2)	1.05 (0.79–1.38)
HPV type 16 incidence	24 (3.2)	15 (2.1)	1.56 (0.83–2.96)
HPV type 18 incidence	11 (1.5)	10 (1.3)	1.10 (0.47–2.57)
HPV type 33 incidence	9 (1.2)	11 (1.5)	0.80 (0.33–1.92)
HPV type 58 incidence	19 (2.6)	15 (2.1)	1.26 (0.65–2.47)
Participants with no HPV detected at baseline (n=1,180)			
Group n	593	587	
One or more new HPV type(s) detected	120 (20.2)	131 (22.3)	0.91 (0.73–1.13)
One or more new oncogenic HPV type(s) detected	56 (9.4)	51 (8.7)	1.09 (0.76–1.56)
HPV type 16 incidence	15 (2.5)	6 (1.0)	2.47 (0.97–6.33)
HPV type 18 incidence	7 (1.2)	6 (1.0)	1.15 (0.39–3.42)
HPV type 33 incidence	6 (1.0)	9 (1.5)	0.66 (0.24–1.84)
HPV type 58 incidence	10 (1.7)	9 (1.5)	1.10 (0.61–1.07)

CI, confidence interval; HPV, human papillomavirus.
Data are n (%) unless otherwise specified.
Populations are not mutually exclusive. Oncogenic human papillomavirus types defined as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.
* Excludes women with no evaluable baseline tests (n=49), no evaluable 12-month test (n=341), untyped human papillomavirus at both baseline and follow-up (n=9), and no postenrollment test due to lost-to-follow-up and/or withdrawal (n=107).

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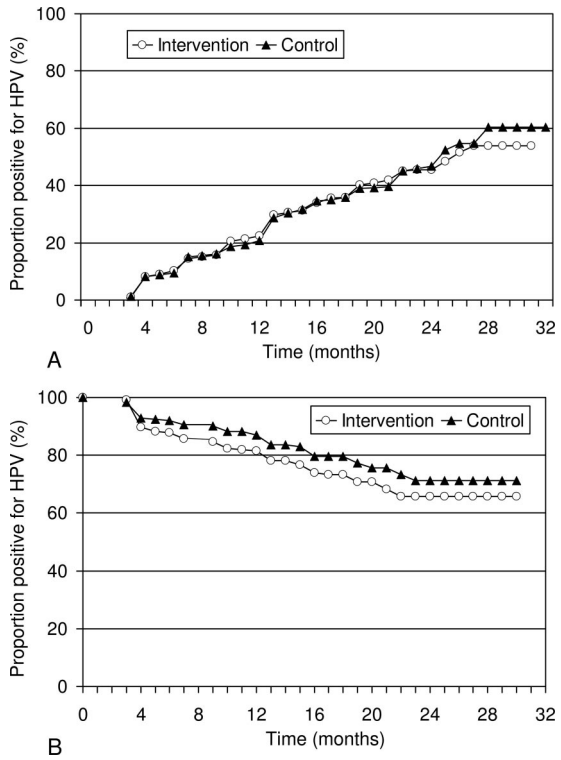

Fig. 2. A. Cumulative incidence of any human papillomavirus (HPV) among women with no HPV detected at baseline, by randomized group. **B.** Clearance of HPV among women with any HPV detected at baseline, by randomized group.

Sawaya. Effect of Diaphragm on HPV. Obstet Gynecol 2008.

using results of both self- and clinician-collected HPV tests among women with no HPV detected at baseline were similar in the two study arms (Fig. 2A, P=.71). Table 4 shows HPV clearance at 12 months and exit by randomized group. For most outcomes, no differences were noted between randomized groups. At 12 months, clearance of oncogenic HPV (to "no HPV detected") and clearance of HPV type 58 were lower in the intervention group; neither difference was statistically significant at exit. Clearance of HPV type 18 was lower at exit in the intervention group.

Using results of both self- and clinician-collected HPV tests, Kaplan-Meier estimates of cumulative HPV clearance probabilities among women with any HPV detected at baseline (to "no HPV detected") and women with any oncogenic HPV detected at baseline (to "no HPV detected") were not significantly different between randomized groups (any HPV, Fig. 2B, P=.16; any oncogenic HPV, P=.72). Estimated cumulative clearance probabilities of HPV type 18 (P=.11) and HPV type 58 (P=.17) were also similar between randomized groups.

Women in the intervention group were more likely to report infrequent condom use, defined as condom use at less than one third of last sex acts (23% compared with 13%, P<.001). At 12 months, about one half of women in the intervention group (50.5%) reported diaphragm/gel use at 100% of prior sex acts; at study exit, this proportion was 34.5%. In "per-protocol" analyses, women reporting diaphragm/gel use at 100% of prior sex acts had a lower likelihood of having one or more new HPV types detected at 12 months (17.8% compared with 23.9%, RR 0.75, 95% CI 0.58–0.96) and exit (21.4% compared with 27.9%, RR 0.77, 95% CI 0.59–0.99) compared with women in the control group. Women in the intervention group with no HPV at baseline had a lower likelihood of having any HPV detected at 12 months (16.2% compared with 22.3%, RR 0.73, 95% CI 0.54–0.98); this difference was not statistically significant at exit (20.0% compared with 25.9%, RR 0.77, 95% CI 0.57–1.05). Human papillomavirus clearance was not affected by consistency of diaphragm/gel use. Expanding our definition of oncogenic HPV to include five additional types yielded similar results.

DISCUSSION

Diaphragm plus lubricant gel provision did not affect HPV incidence or clearance among women receiving risk reduction counseling and condoms in an HIV prevention program. Although our findings do not support the protective effects of diaphragm use on HPV infection reported in observational studies, the specific context in which this study was performed may limit its generalizability to other settings. Although restricting analyses to women with high adherence to diaphragm/gel use showed some protection from incident HPV infections, these data must be interpreted with caution due to the potential for substantial confounding with subgroup analyses, especially because a large proportion of women in the intervention group were excluded from these analyses.

Decreased clearance of HPV types 18 and 58 was noted at the two predefined time points among women in the intervention group. These differences were not statistically significant over the course of the entire trial; a higher proportion of women with HPV type 18 at baseline in the intervention group may have accounted for the HPV type 18–related observation. Of note, type-specific analyses were limited by small numbers of outcomes and subsequent low statistical power. Given that women in the intervention group were more likely to report infrequent condom use, these observed differences may have been due to

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Table 4. Human Papillomavirus Clearance at 12 Months and Exit Among Women With Any Human Papillomavirus Type(s), Any Oncogenic Human Papillomavirus Type(s), and/or Human Papillomavirus Types 16, 18, 33, or 58 Detected at Baseline*

Populations, Outcomes, and Time Points	Group Assignment [n/N (%)]		Relative Risk (95% CI), Intervention vs Control
	Intervention	Control	
Participants with any HPV type(s) detected at baseline			
No HPV detected			
At 12 months	59/181 (32.6)	74/182 (40.7)	0.80 (0.61–1.05)
At exit	97/164 (59.1)	105/168 (62.5)	0.95 (0.80–1.12)
Nondetection of ≥1 HPV type(s) detected at baseline			
At 12 months	118/179 (65.9)	123/175 (70.3)	0.94 (0.81–1.08)
At exit	130/164 (79.3)	124/168 (73.8)	1.07 (0.95–1.21)
Participants with any oncogenic HPV type(s) detected at baseline			
No HPV detected			
At 12 months	33/122 (27.0)	49/121 (40.5)	0.67 (0.46–0.96)
At exit	37/111 (33.3)	47/109 (43.1)	0.77 (0.55–1.09)
No oncogenic HPV detected			
At 12 months	57/122 (46.7)	70/121 (57.9)	0.81 (0.63–1.03)
At exit	61/111 (55.0)	63/109 (57.8)	0.95 (0.75–1.20)
Participants with HPV type(s) 16, 18, 33 and/or 58 detected at baseline			
No HPV type 16 detected			
At 12 months	21/33 (63.6)	19/40 (47.5)	1.34 (0.88–2.03)
At exit	17/26 (65.4)	17/33 (51.5)	1.27 (0.82–1.96)
No HPV type 18 detected			
At 12 months	8/20 (40.0)	8/11 (72.7)	0.55 (0.29–1.05)
At exit	9/18 (50.0)	11/12 (91.7)	0.55 (0.33–0.89)
No HPV type 33 detected			
At 12 months	7/13 (53.8)	14/18 (77.8)	0.69 (0.40–1.21)
At exit	10/13 (76.9)	9/15 (60.0)	1.28 (0.77–2.13)
No HPV type 58 detected			
At 12 months	23/43 (53.5)	28/35 (80.0)	0.67 (0.48–0.92)
At exit	30/38 (78.9)	28/33 (84.8)	0.93 (0.75–1.16)

CI, confidence interval; HPV, human papillomavirus.
Participants are counted only once within each applicable row. Some participants are counted in more than one row. Oncogenic human papillomavirus types defined as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.
* Includes women with evaluable samples at baseline and 12 months and/or exit.

less condom use among women in the intervention arm or due to actual use of the diaphragm/gel.

Our study has several limitations. We could only estimate HPV incidence and clearance within each arm because we had a maximum of three time points when clinician-collected swabs were obtained; some HPV tests may have been either falsely positive or falsely negative such that true incidence and clearance may have been either underestimated or overestimated. Errors due to false-positive and false-negative testing, however, would be expected to occur equally between the two groups because of randomization; the relative comparisons should reflect valid differences between groups. Our intervention was diaphragm/gel provision, and we could not fully ascertain how often and how correctly participants used the study products because we relied only on self-report; poor adherence to diaphragm/gel use may have accounted for the null effect observed. Because the trial could not be blinded, assignment to the intervention group seems to have had an effect on condom use, and may have had an effect on reporting of study product use. Numerous other explanations based on equally plausible differences due to knowledge of the group assignment may also explain our findings. Another plausible explanation for our observed lack of effect may be a beneficial effect of the intervention on HPV that was offset by a detrimental effect due to concurrent decrease in the use of condoms among women in the intervention group.

Study strengths include its randomized design, large size, and small numbers of participants lost to follow-up. We were able to exclude potential effects of the lubricant gel on HPV detection based on

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studies we conducted before completion of the trial.[21]

Because of the ethical imperative to offer condoms to both arms in this trial of HIV seroconversion, we could only estimate the marginal benefit of diaphragm/gel provision beyond that provided by condoms alone. Given evidence demonstrating benefit of condoms for clearance of HPV infection,[17] additional benefit contributed by diaphragm/gel may not have been measurable. Our findings in the per-protocol analysis and the importance of female-controlled methods of prevention of sexually transmissible infections, however, indicate that further study of diaphragms for the prevention of HPV and HPV-related diseases may be warranted.

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