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Cervical HPV Natural History Among Young Western Cape, South African Women: The Randomized Control EVRI Trial

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Abstract

Objective—The objective of this analysis was to assess human papillomavirus (HPV) infection persistence and incidence 7-months post-enrollment by HPV vaccine study arm (vaccine or placebo).

Methods—HIV-negative, sexually active women aged 16–24 years in the Western Cape, South Africa, were enrolled in the EVRI Trial and were randomized to receive 4-valent HPV vaccine or placebo. Cervical specimens were collected at enrollment and at the 7-month visit and were genotyped for HPV. HPV prevalence, persistence, and incidence were calculated. Prevalence ratios and odds ratios were calculated to assess factors associated with a prevalent and incident HPV infection.

Results—HPV incidence rates were marginally higher for the placebo group (n=163) compared to the vaccine group (n=169). A large proportion of the prevalent high risk (HR-HPV) HPV types (49%) persisted over the 7-month period in both arms. Prevalent HR-HPV infection was

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Conflicts of Interest

A.R.G. is on the Speaker's Bureau of Merck. M.F.S.v.d.L. received research funding from Sanofi-Pasteur MSD; he is a co-investigator in a Sanofi-Pasteur-MSD HPV vaccine trial; he sat on a vaccine advisory board of GSK. For the remaining authors, no conflicts of interest were declared.

significantly associated with a prevalent gonorrhea infection and detection of Herpes simplex type 2 antibodies. Incident HR-HPV infection was significantly associated with abnormal cervical cytology at enrollment and younger age.

Conclusions—Women living in geographic areas, such as southern Africa, at high-risk for HPV need to receive HPV vaccination at a very young age to maximally prevent infection and subsequent disease.

Keywords

HPV vaccine; clinical trial; EVRI; STIs

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI), one that can infect multiple anatomic sites in both men and women. Persistent HPV infection is the necessary cause of cervical cancer and causes 90% of anal, 50% of penile, 43% of vulvar, 70% of vaginal, and 33-72% oropharyngeal cancers worldwide.[1, 2] Women and men residing in southern African countries have among the highest burden of HPV infection and related cancers worldwide.[3-6]

There are two licensed HPV vaccines that are highly efficacious in preventing 70% of cervical disease among women through protection against HPV16 and HPV18 infections. Recently a 9-valent HPV vaccine was licensed in the United States that increases prevention of cervical disease to 90% through the protection from HPV types 16, 18, 31, 33, 45, 52, and 58.[7] The uptake of the vaccine is of major public health importance, especially in countries that have no or poor cervical cancer screening programs.

Within the context of a Phase II Trial to assess the feasibility of conducting a placebo-controlled randomized HPV vaccine trial to prevent HIV infection, we assessed cervical HPV status at enrollment and 7 months post-enrollment among women at high-risk for HIV.

MATERIALS AND METHODS

Population

Women residing in the Western Cape, South Africa were enrolled from November 2012 to July 2013 in a preparedness study, the Efficacy of HPV Vaccine to Reduce HIV Infection (EVRI) Trial (NCT01489527). A full description of study procedures and conduct of the trial has been published elsewhere.[8] Briefly, women aged 16-24 that were HIV-negative and non-pregnant were enrolled in a Phase II randomized controlled trial of Gardasil (4-valent HPV (4vHPV) vaccine) vs. placebo (saline).

Trial-eligible women were randomized 1:1 to receive 4vHPV or placebo vaccines. All staff and study investigators were blinded to participants' vaccine status. Vaccine was administered at enrollment, month 2, and month 6. Study participants were followed for one month after the last vaccine dose (through month 7). At the 7-month visit, individual

unblinding occurred, and women randomized to the placebo group were offered Gardasil vaccine.

This study was conducted in accordance with ethics committee review and approved by the Institutional Review Boards of The University of South Florida and Stellenbosch University. South African policies and ethics approval regarding parental permission for children to take part in research studies were followed.

Study Protocol

At each follow-up visit after randomization, urine pregnancy tests and rapid HIV tests were performed. Women with positive pregnancy tests were referred to care and removed from the study. Women with a positive rapid HIV test were retested with two different confirmatory tests. Participants with a confirmed positive HIV test after the enrollment visit were referred to care and remained on trial.[9] However, HIV-positive women (n=3) post-enrollment were removed from the current analysis as HIV is known to influence HPV natural history.[10] At the enrollment and 7-month visits, sexual history, health, and sociodemographic characteristics were assessed by a tablet-based questionnaire using a computer-assisted self-interview available in English, Xhosa, and Afrikaans.

A speculum exam of the vagina and cervix was conducted and, after collection of specimens, a digital exam was performed. Samples obtained from the vulva/labia and endocervical/ectocervical specimens for HPV detection were obtained at the enrollment and 7-month visits using a pre-wetted Dacron swab placed in an STM collection vial (Digene Hybrid Capture test kit). Specimens for HPV analysis were archived at 4°C prior to testing. Cervical cytology specimens were obtained at enrollment using the SurePath method. If the Pap cytology results were greater than atypical squamous cells of undetermined significance (ASCUS)/low-grade squamous intraepithelial lesions (LSIL), the participant was referred to the local clinic for a repeat Pap cytology and further clinical management as indicated. If the Pap cytology results were high-grade squamous intraepithelial lesions (HSIL), the participant was referred to the study gynecologist (HB) for colposcopy and clinical management as indicated.

Laboratory Analyses

For HPV analyses, DNA was extracted from cervical cell specimens using the Qiagen Media Kit and amplified by polymerase chain reaction (PCR) with the PGMY09/11 L1 consensus primer system and AmpliTaq Gold polymerase (Perkin-Elmer). HPV genotyping was conducted on all specimens, regardless of PCR results, using the Linear Array HPV Genotyping Test (Roche Diagnostics), which detects 37 HPV genotypes (high-risk (HR-HPV): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68; low-risk (LR-HPV): 6, 11, 26, 40, 42, 53-55, 61, 62, 64, 66, 67, 69-73, 81, 82, 83, 84, 89, IS39).[11] The Linear Array method cannot detect HPV 52 co-infections in the presence of HPV 33, 35, or 58, so some HPV 52 co-infections may have gone undetected. Five participants with an inadequate amount of sample for HPV detection and six participants that had HPV β -globin negative samples at the enrollment visit were removed from analyses. At the 7-month visit, only two participants had an inadequate amount of sample for HPV testing; specimens from the remaining

participants were all β -globin positive. Therefore the final sample size for this analysis was 332 women (vaccine arm n=169 and placebo arm n=163).

Statistical Analysis

The vaccine and placebo groups were compared using the enrollment visit demographic and behavioral characteristics using Pearson Chi-squared tests for categorical variables and Mann-Whitney for continuous variables, with p-values computed using Monte Carlo methods. Cervical cytology was categorized as normal (i.e., normal or ASCUS) and abnormal (i.e., LSIL or HSIL).

HPV period prevalence and incidence were calculated separately by treatment group (vaccine, placebo) for the four HPV types in the vaccine (6/11/16/18). The two vaccine groups were combined for the other 33 HPV types when estimating HPV period prevalence and incidence.[12] Period prevalence was defined as having a specific HPV type at either enrollment or the 7-month visit. A persistent infection was defined as having a specific HPV type at both enrollment and the 7-month. Persistent infections were evaluated by combining both vaccine treatment arms as the 4vHPV vaccine is not expected to have a therapeutic effect on persistent infection. An incident infection was defined as the presence of a type-specific infection at the 7-month visit when that HPV type was absent at enrollment. Person time was calculated as the time from specimen collection at enrollment to the date of the 7-month specimen collection. The incidence rate and 95% confidence interval (95% CI) was estimated assuming the number of incident events followed a Poisson distribution. Incidence rate ratios (IRR) and p values were also calculated based on the Poisson assumption. To assess factors associated with prevalent cervical HPV infection, prevalence ratios (PRs) and 95% CI were calculated with Poisson regression using robust variance estimation. Separate models for factors associated with prevalent infections were estimated for two HPV outcomes: 1.) women with at least one HRHPV infection vs HPV-negative women and 2.) women with only a LR-HPV infection vs HPV-negative women. Backwards elimination was utilized to assess factors independently associated with HPV prevalence with final models adjusted for cervical cytology, lifetime number of partners, and age category (16-18, 19-21, 22-24 years). Odds ratios (ORs) and 95% CI were calculated using logistic regression to assess factors associated with an incident HR-HPV infections (n=128) compared to women without an incident HPV infection (n=103), excluding women with only an incident HPV16 or HPV18 infection (n=12) as these HPV types are included in the 4vHPV vaccine. Backwards elimination was used to determine factors independently associated with incident HPV infection with final models adjusted for cervical cytology, lifetime number of partners, age category (16-18, 19-21, 22-24 years), and vaccine group.

RESULTS

The vaccine treatment groups were similar with respect to their enrollment demographic characteristics (Table 1). However, women randomized to receive the HPV vaccine were more likely to have ever been pregnant, have more male lifetime sexual partners, and have abnormal cervical cytology compared to women randomized to receive the placebo. Although women reported a wide range of number of lifetime sexual partners, the median

number of partners reported was only two among those receiving placebo and three among those receiving active vaccine.

Cervical HPV Prevalence

HPV type 6, 11, 16, 18 prevalence did not differ significantly between study arms (Table 1). The most commonly detected HR-HPV genotypes (excluding the four HPV vaccine types) over the 7- month observation period among the vaccine and placebo groups were HPV51 (16.6%), HPV52 (16.3%), HPV58 (16.0%), and HPV35 (15.4%) (Table 2). Among the LRHPV types, HPV61 (11.3%) and HPV62 (13.5%) were the most commonly occurring during the 7-month observation period (Table 2).

7-month Cervical HPV Incidence

Participant median follow-up time was 6.6 months for the vaccine group and 6.4 months for the placebo group. Among the combined cohort of women, HPV incidence rates (nonvaccine types) were highest for HR-HPV types 51 (13.5 per 1000pm) and 59 (11.5 per 1000pm) and for LR-HPV types 62 (13.5 per 1000pm) and 84 (11.4 per 1000 pm) (Table 2). The vaccine group had a marginally significantly lower rate of HPV 6 (2.8 vs. 7.3 per 1,000 person-months (1000pm)) and 18 (2.8 vs. 7.5 per 1000pm) acquisition compared to the placebo group (Table 3). Incidence rates for HPV types 16 and 11 were comparable between study arms.

Cervical HPV Persistence

A large proportion (49.0%) of the HR-HPV types present at enrollment persisted over the 7-month period (Table 4). HR-HPV 7-month persistence ranged from 63.6% for HPV58 to 0.0% for HPV33. The 7-month persistence for HPV16 and HPV 18 was 43.1% and 57.9%, respectively. LR-HPV 7-month persistence was also common ranging from 71.4% for HPV39 to 0% for HPV40 and HPV64. HPV6 and 11 7-month persistence was 45.5% and 66.7%, respectively.

Factors Associated with HPV Infection

Factors associated with prevalent infection—We assessed factors associated with a prevalent HPV infection among participants at the enrollment visit, regardless of vaccine arm (n=332; Table 5). Prevalence of HR-HPV infection at enrollment was independently associated with presence of antibodies to HSV2 (adjusted PR (aPR) = 1.25, 95%CI= 1.07-1.47) and current gonorrhea infection (aPR= 1.45, 95%CI= 1.21-1.73) after adjusting for cytology, age, and lifetime number of partners (Table 5). LR-HPV infection was independently associated with abnormal cytology (aPR= 2.88, 95%CI= 1.53-5.42) after adjusting for age and lifetime number of partners. Prevalence of a 4vHPV type at enrollment was associated with a current chlamydia infection (aPR=1.69, 95% CI=1.15-2.49) after adjusting for cytology, age, and lifetime number of partners.

Factors at enrollment associated with acquisition of new HPV infection—

Women who acquired a new HR-HPV infection were significantly younger in age (16-18 vs. 22-24, aOR=2.55, 95%CI= 1.19-5.47) and were also significantly more likely to have had

abnormal cervical cytology (aOR=3.40, 95% CI= 1.27-9.10) at enrollment compared to women who did not acquire a new HPV infection, after controlling for lifetime number of sexual partners and vaccine group (Table 6).

DISCUSSION

We have described the incidence, prevalence and persistence of cervical HPV among young South African women participating in randomized placebo controlled HPV vaccine trial. The study arms were comparable in their enrollment demographic characteristics and prevalence of vaccine HPV types (6/11/16/18). Prevalence and incidence of cervical HPV was very high in this study population of women residing in a community of high HIV prevalence. The data presented here clearly demonstrate rapid cervical HPV acquisition after sexual debut and highlights the need for early HPV interventions.

HPV prevalence and incidence were higher than documented in other studies of women internationally. We previously reported that 71% of our study participants regardless of study arm had at least one HPV type at enrollment and 22% were positive for at least one of the HPV types in 4-valent vaccine.[8] This prevalence of any HPV type of 71% is comparable to HPV prevalence observed among female sex workers and HIV-positive women in Africa (39%-75%).[13] HPV16 point and period prevalence among women in our cohort was 15% and 17% respectively, comparable to only one other cohort of HIV-negative women studied in Cape Town, South Africa (16%).[14] HPV incidence rates among our study population were higher than that reported from other HIV-negative populations. For example, the HPV16 incidence rate in this study was 6.8 per 1000 pm (vaccine IR=7.0 per 1000 pm and placebo IR=6.6 per 1000 pm). This compares to an HPV16 incidence rate in the general population of 1.4 per 1000 pm among a Brazilian cohort [15] to a high estimate of 5.9 per 1000 pm among young women in the United States.[16] Among women who are at high-risk for HIV, but HIV-negative, an HPV 16 incidence rate of 1.39 per 1000 pm was observed, and among HIV-positive women, an HPV 16 incidence rate of 2.16 per 1000 pm was observed.[17]

Persistence of prevalent infections was also very high in this population; however, the prevalence of cervical abnormalities was relatively low given the high HPV prevalence and persistence observed. Overall 12% of participants had a low grade squamous intraepithelial lesion (LSIL) and one participant had a high grade squamous intraepithelial lesion (HSIL) at enrollment.[8] This low prevalence may reflect that the infections detected were relatively recently acquired, not allowing sufficient infection duration for us to observe progression to lesions, especially HSIL.

The risk of cervical malignancy is not the only concern for HPV infection as it might also increase the risk for HIV acquisition.[18-22] Studies conducted among women and men consistently demonstrate increased risk of HIV with prior anogenital HPV infection.[23-29] If this is correct, the high prevalence and incidence of cervical HPV in this population indicate that these young women are at high risk of HIV infection. In fact HIV prevalence data from these communities indicate that 29.5% of antenatal care clinic attendees aged 15-49 years are HIV seropositive.[30]

There are several strengths and limitations to the current study that need to be considered in interpreting the data presented. HPV was only detected at enrollment and at the 7-month visit; therefore it is unknown when a woman acquired the HPV infection compared to receiving each dose of the vaccine. The 4vHPV vaccine is prophylactic and there is no protective effect against clinical endpoints among women who had already been infected prior to vaccination. In this current study where data are only available one month post-vaccination we cannot draw conclusions about clinical efficacy to prevent HPV infection, HPV-related disease or HIV. Clinical efficacy of HPV vaccine trials requires longer follow-up to determine prevention of a persistent HPV infection. Our trial does not have the necessary follow-up needed to determine clinical efficacy of the HPV vaccine. Our findings may not be generalizable to all South African women and likely do not represent STI and risk conditions of women in other sub-Saharan countries.

HPV prevalence, incidence, and persistence were high among these young women despite having few reported lifetime male sexual partners. Our data suggest the need for early HPV vaccination of younger (ages 9-12 years) rather than older adolescent females (ages 13-18 years) residing in HPV/HIV high risk communities. Ideally, we need to include both genders in STI and HIV prevention efforts to have the greatest impact on prevention HPV infection and subsequent disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1Enrollment demographic and sexual health characteristics of women^a in the EVRI Trial

	Vaccine (n=169)	Placebo (n=163)	P-value ^b
Median age in years (range)	20 (16-24)	20 (16-24)	0.17
Survey language			0.44
English	160 (94.7)	159 (97.5)	
Xhosa	3 (1.8)	1 (0.6)	
Afrikaans	6 (3.6)	3 (1.8)	
Marital status			
Single/Widowed	163 (96.4)	157 (96.3)	1.00
Married/Living Together	6 (3.6)	6 (3.7)	
Education			0.39
Grade 7	7 (4.1)	9 (5.5)	
Grade 8-12	97 (57.4)	86 (52.8)	
Passed Grade 12	36 (21.3)	29 (17.8)	
Some college/tech	29 (17.2)	39 (23.9)	
Median age of first vaginal sex (range)^c	17 (1-21)	17 (13-21)	0.48
Current birth control use			
Oral Contraceptives	8 (4.7)	3 (1.8)	0.21
IUD/Loop/Coil	1 (0.6)	1 (0.6)	1.00
Depo Provera	43 (25.4)	41 (25.2)	1.00
Condoms	37 (21.9)	38 (23.3)	0.80
Ever been pregnant	95 (56.2)	70 (42.9)	0.02
Lifetime no. of male sexual partners^c; median (range)	3 (1-22)	2 (1-24)	0.006
1	21 (12.4)	29 (17.8)	
2	35 (20.7)	38 (23.3)	
3+	80 (47.3)	49 (30.1)	
Unknown	33 (19.5)	47 (28.8)	
Number of sexual partners in the past 6 months^c; median (range)	1 (0-5)	1 (0-5)	0.43
0	8 (4.7)	6 (3.7)	
1	77 (45.6)	65 (39.9)	
2	10 (5.9)	16 (9.8)	
3+	6 (3.6)	3 (1.8)	
Unknown	68 (40.2)	73 (44.8)	
Ever received presents/money/drugs for sex	7 (4.1)	5 (3.1)	0.77
Diagnosis of STI			
Gonorrhea	15 (8.9)	20 (12.3)	0.37
Chlamydia	58 (34.3)	53 (32.5)	0.81
Herpes Simplex	74 (43.8)	77 (47.2)	0.58
Syphilis	14 (8.3)	8 (4.9)	0.27
Cervical Cytology			0.02

		Vaccine (n=169)	Placebo (n=163)	P-value ^b
HPV prevalence at enrollment	Normal	142 (84.0)	151 (92.6)	
	Abnormal	27 (16.0)	12 (7.4)	
	6	8 (4.7)	3 (1.8)	0.22
	11	2 (1.2)	1 (0.6)	1.00
	16	21 (12.4)	30 (18.4)	0.18
	18	10 (5.9)	9 (5.5)	1.00

^aWomen who had valid HPV DNA results at both enrollment and Month 7 visits

^bPvalues were calculated based on Pearson chi-square and Mann-Whitney tests

^cSample size reduced due to errors in reporting sexual behavior: placebo (n=116) and vaccine (n=138)

Table 2
Period Prevalence and Incidence of non-vaccine HPV types among women in the EVRI trial

	Period prevalence, No. (%) ^a	Women at risk, No. ^b	Women with infection, No. ^c	Person-months	Incidence rate (95% CI) ^d
High Risk					
31	24 (7.2)	316	8	2150	3.7 (1.9-6.7)
33	11 (3.3)	327	6	2221	2.7 (1.3-5.3)
35	51 (15.4)	302	21	2058	10.2 (6.7-15.0)
39	23 (6.9)	319	10	2167	4.6 (2.5-7.9)
45	35 (10.5)	310	13	2112	6.2 (3.6-9.9)
51	55 (16.6)	305	28	2069	13.5 (9.4-19.0)
52	54 (16.3)	296	18	2005	9.0 (5.7-13.6)
56	24 (7.2)	321	13	2179	6.0 (3.5-9.6)
58	53 (16.0)	299	20	2043	9.8 (6.4-14.5)
59	47 (14.2)	309	24	2094	11.5 (7.7-16.5)
68	30 (9.0)	310	8	2107	3.8 (2.0-6.9)
Low Risk					
26	15 (4.5)	325	8	2210	3.6 (1.9-6.5)
40	17 (5.1)	326	11	2216	5.0 (2.8-8.3)
42	18 (5.4)	327	13	2218	5.9 (3.5-9.5)
53	41 (12.4)	312	21	2123	9.9 (6.5-14.6)
54	34 (10.2)	311	13	2119	6.1 (3.6-9.9)
55	26 (7.8)	320	14	2178	6.4 (3.9-10.2)
61	54 (16.3)	301	23	2045	11.3 (7.5-16.3)
62	54 (16.3)	306	28	2079	13.5 (9.3-18.9)
64	3 (0.9)	331	2	2247	0.9 (0.3-2.5)
66	38 (11.5)	308	14	2079	6.7 (4.0-10.7)
67	10 (3.0)	327	5	2221	2.3 (1.0-4.6)
69	10 (3.0)	329	7	2233	3.1 (1.6-5.9)
70	29 (8.7)	319	16	2167	7.4 (4.6-11.4)
71	4 (1.2)	328	0	2228	N.E.
72	11 (3.3)	328	7	2224	3.2 (1.6-5.9)

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	Period prevalence, No. (%) ^a	Women at risk, No. ^b	Women with infection, No. ^c	Person-months	Incidence rate (95% CI) ^d
73	27 (8.1)	321	16	2176	7.4 (4.6-11.4)
81	40 (12.1)	306	14	2087	6.7 (4.0-10.7)
82	19 (5.7)	322	9	2186	4.1 (2.2-7.2)
83	39 (11.8)	315	22	2141	10.3 (6.8-15.0)
84	45 (13.6)	311	24	2112	11.4 (7.7-16.3)
89	40 (12.1)	311	19	2115	9.0 (5.8-13.5)
IS39	14 (4.2)	325	7	2207	3.2 (1.6-5.9)

Abbreviations: CI: Confidence Interval; HPV: human papillomavirus; HR: High Risk HPV Type; LR: Low Risk HPV type; N.E.: Not estimable

^aThe number and proportion of women with type-specific HPV infection at either enrollment or the 7-month visit.

^bThe number of women negative for a specific HPV type at the enrollment visit.

^cThe number of women negative for a specific HPV type at the enrollment visit and positive for that specific HPV type at the 7-month visit.

^dThe number of infections per 1000 person-months.

Table 3

Period Prevalence and Incidence of vaccine HPV types by study arm among women in the EVRI trial

HPV	Vaccine (n=169)				Placebo (n=163)				p value ^e		
	Period prevalence No. (%) ^a	Women at risk, No. ^b	Women with infection No. ^c	Person-months	Incidence rate (95% CI) ^d	Period prevalence No. (%) ^a	Women at risk, No. ^b	Women with infection, No. ^c		Person-months	Incidence rate (95% CI) ^d
6	11(6.5)	161	3	1077	2.8(1.0-6.7)	11(6.8)	160	8	1103	7.3(3.7-13.1)	0.13
11	5(3.0)	167	3	1119	2.7(1.0-6.5)	5(3.1)	162	4	1116	3.6(1.5-7.9)	0.70
16	28(16.6)	148	7	993	7.0(3.5-13.1)	36(22.1)	133	6	915	6.6(3.1-12.8)	0.90
18	13(7.7)	159	3	1067	2.8(1.0-6.8)	17(10.4)	154	8	1063	7.5(3.9-13.6)	0.12

Abbreviations: CI: Confidence Interval; HPV: human papillomavirus;

^aThe number and proportion of women with type-specific HPV infection at either enrollment or the 7-month visit.

^bThe number of women negative for a specific HPV type at the enrollment visit.

^cThe number of women negative for a specific HPV type at the enrollment visit and positive for that specific HPV type at the 7-month visit.

^dThe number of infections per 1000 person-months.

^eP values were calculated based on Poisson regression comparing the incidence rate between vaccine and placebo for each HPV type

Table 4

Type-Specific HPV Persistence Among Women in the EVRI Trial

HPV	Prevalent at baseline No.	Persisted No (%)
High-Risk		
16	51	22(43.1)
18	19	11(57.9)
31	16	6(37.5)
33	5	0(0.0)
35	30	18(60.0)
39	13	8(61.5)
45	22	11(50.0)
51	27	11(40.7)
52	36	19(52.8)
56	11	4(36.4)
58	33	21(63.6)
59	23	11(47.8)
68	22	9(40.9)
Low-Risk		
6	11	5(45.5)
11	3	2(66.7)
26	7	3(42.9)
40	6	0(0.0)
42	5	1(20.0)
53	20	10(50.0)
54	21	8(38.1)
55	12	5(41.7)
61	31	20(64.5)
62	26	13(50.0)
64	1	0(0.0)
66	24	9(37.5)
67	5	2(40.0)
69	3	1(33.3)
70	13	3(23.1)
71	4	1(25.0)
72	4	1(25.0)
73	11	4(36.4)
81	26	11(42.3)
82	10	6(60.0)
83	17	8(47.1)
84	21	6(28.6)
89	21	4(19.1)
IS39	7	5(71.4)

Table 5
Factors at enrollment associated with prevalent HPV infection among women in the EVRI Trial

	HR-HPV (n=278) ^d		LR-HPV (n=144) ^b		4vHPV (n=76) ^c	
	uPR (95% CI)	aPR (95% CI) *	uPR (95% CI)	aPR (95% CI) *	uPR (95% CI)	aPR (95% CI) *
Age in years						
22-24	ref	ref	ref	ref	ref	ref
19-21	1.03(0.84-1.26)	0.94(0.78-1.14)	0.60(0.37-0.98)	0.63(0.39-1.03)	1.08(0.65-1.79)	0.92(0.55-1.53)
16-18	1.09(0.87-1.37)	0.99(0.79-1.24)	0.89(0.54-1.49)	1.06(0.63-1.77)	1.63(0.97-2.75)	1.31(0.78-2.2)
Survey language						
English	ref		ref		ref	
Xhosa/Afrikaans	0.73(0.41-1.29)		0.37(0.06-2.29)		0.66(0.18-2.41)	
Marital status						
Single/Widowed	ref		ref		ref	
Married/Living Together	0.66(0.35-1.27)		0.37(0.06-2.29)		0.36(0.05-2.35)	
Education						
Grade 7	ref		ref		ref	
Grade 8-12	1.73(0.88-3.41)		1.08(0.47-2.5)		0.94(0.39-2.28)	
Passed Grade 12	1.43(0.71-2.89)		0.71(0.27-1.9)		0.74(0.27-1.99)	
Some college/tech	1.64(0.82-3.29)		1.24(0.52-2.97)		1(0.39-2.57)	
Birth Control Used						
Yes	ref		ref		ref	
No	1.03(0.88-1.22)		0.99(0.65-1.51)		1.26(0.84-1.88)	
Pregnant						
Never	ref		ref		ref	
Ever	0.87(0.74-1.02)		0.89(0.58-1.35)		1.01(0.68-1.5)	
Lifetime no. of male sexual partners						
1	ref	ref	ref	ref	ref	ref
2	1.05(0.80-1.39)	1.00(0.77-1.30)	1.49(0.61-3.67)	1.9(0.86-4.19)	0.95(0.51-1.76)	0.95(0.51-1.78)
3+	1.15(0.90-1.47)	1.15(0.92-1.45)	2.02(0.89-4.56)	2.63(1.31-5.28)	0.69(0.38-1.25)	0.72(0.4-1.29)

	HR-HPV (n=278) ^a		LR-HPV (n=144) ^b		4vHPV (n=76) ^c	
	uPR (95% CI)	aPR (95% CI) *	uPR (95% CI)	aPR (95% CI) *	uPR (95% CI)	aPR (95% CI) *
Unknown	0.93(0.69-1.24)	0.91(0.70-1.19)	1.36(0.56-3.31)	1.59(0.77-3.28)	1.06(0.59-1.9)	1.1(0.62-1.95)
Ever received presents/money/drugs for sex						
No	ref		ref		ref	
Yes	0.82(0.45-1.47)		1.15(0.48-2.78)		0.72(0.2-2.59)	
Laboratory Diagnosis of Gonorrhea						
No	ref	ref	ref		ref	
Yes	1.39(1.20-1.62)	1.45(1.21-1.73)	1.57(0.79-3.09)		1.75(1.08-2.84)	
Laboratory Diagnosis of Chlamydia						
No	ref		ref		ref	ref
Yes	1.22(1.04-1.43)		0.95(0.58-1.56)		1.79(1.22-2.64)	1.69(1.15-2.49)
Laboratory Diagnosis of Herpes Simplex						
No	ref	ref	ref		ref	
Yes	1.22(1.04-1.43)	1.25(1.07-1.47)	1.48(0.98-2.25)		0.92(0.62-1.37)	
Laboratory Diagnosis of Syphilis						
No	ref		ref		ref	
Yes	1.14(0.86-1.5)		1.53(0.82-2.86)		1.43(0.75-2.73)	
Cervical Cytology						
Normal	ref	ref	ref	ref	ref	ref
Abnormal	1.47(1.30-1.67)	1.52(1.32-1.75)	2(1.19-3.36)	2.88(1.53-5.42)	2.16(1.42-3.31)	2.19(1.46-3.3)

* Backward selected model forced in Cytology, Age, and lifetime partners into aPR. Abbreviations: HPV: human papillomavirus; uPR: unadjusted prevalence ratio; aPR: adjusted prevalence ratio; 95% CI: 95% Confidence Interval; ref: reference group

^a Prevalent HR-HPV vs. negative for all HPV types

^b Prevalent LR-HPV only vs. negative for all HPV types

^c Prevalent 4vHPV vs negative for all HPV types

Table 6Factors at enrollment associated with incident HR-HPV infection in the EVRI Trial^a

	uOR (95% CL) ^b	aOR (95% CL) ^c
Age		
22-24	ref	ref
19-21	1.52(0.83-2.77)	1.57(0.84-2.93)
16-18	2.36(1.14-4.91)	2.55(1.19-5.47)
Survey language		
English	ref	
Xhosa/Afrikaans	0.52(0.14-1.9)	
Marital status		
Single/Widowed	ref	
Married/Living Together	0.22(0.04-1.07)	
Education		
Grade 7	ref	
Grade 8-12	0.62(0.17-2.23)	
Passed Grade 12	0.75(0.19-2.95)	
Some college/tech	0.87(0.23-3.35)	
Birth Control Used		
yes	ref	
no	0.82(0.49-1.38)	
Pregnant		
Never	ref	
Ever	1.09(0.65-1.84)	
Lifetime no. of male sexual partners		
1	ref	ref
2	1.04(0.44-2.47)	1.19(0.49-2.94)
3+	1.09(0.49-2.41)	1.52(0.66-3.53)
Unknown	1.28(0.54-3.01)	1.48(0.61-3.59)
Ever received presents/money/drugs for sex		
no	ref	
yes	0.47(0.11-2.02)	
Clinical Diagnosis of Gonorrhea		
no	ref	
yes	1.68(0.65-4.34)	
Clinical diagnosis of Chlamydia		
no	ref	
yes	1.8(1.03-3.17)	
Clinical Diagnosis of Herpes Simplex		
no	ref	
yes	1.07(0.63-1.8)	
Clinical Diagnosis of Syphilis		

	uOR (95% CL) ^b	aOR (95% CL) ^c
no	ref	
yes	0.38(0.13-1.14)	
Cervical Cytology		
Normal	ref	ref
Abnormal	2.99(1.16-7.76)	3.4(1.27-9.10)
Randomized Group		
Gardasil	ref	ref
Placebo	1.09(0.65-1.82)	1.17(0.67-2.02)

Abbreviations: HPV: human papillomavirus; uOR: unadjusted odds ratio; 95% CL: 95% Confidence Limits; aOR: adjusted odds ratio; ref: reference group; N.A.: not applicable

^aWomen with an incident HR-HPV infection^a (n=128), excluding women with only an incident HPV16 or HPV18 infection at the 7-month visit vs. women without any incident HPV infection (n=103)

^bLogistic regression.

^cBackward selection logistic model forced in age, lifetime number of sexual partners, cytology, and randomized group.