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High Baseline Anal HPV and Abnormal Anal Cytology in a Phase 3 Trial of the Quadrivalent HPV Vaccine in HIV-infected individuals over 26 years old: ACTG 5298

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Abstract

Background—The quadrivalent human papillomavirus (HPV) vaccine (qHPV; types 6, 11, 16, 18) is indicated for men and women 9–26 years to prevent HPV associated anogenital high grade squamous intraepithelial lesions (HSIL) and cancer. ACTG 5298 was a randomized placebo controlled Phase 3 study in HIV-infected men who have sex with men (MSM), and women of qHPV to prevent persistent anal HPV infection. Baseline data is presented here.

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Conflict of Interest:

RD Cranston has received institutional grant support from Merck and Co. T Wilkin has received institutional grant support from Gilead, BMS and GlaxoSmithKline/ViiV, and consulting support from GlaxoSmithKline/ViiV. M Cespedes has received institutional grant support from GlaxoSmithKline and consulting support from Gilead.

Methods—HIV-infected MSM, and women 27 years without previous anogenital or oral cancer were enrolled. Baseline anal cytology, high resolution anoscopy and collection of anal, oral, and vaginal specimens for HPV genotyping were performed and acceptability assessed.

Results—575 participants were enrolled (82% male and 18% female). Median age was 47 years. Race/ethnicity was 46% White, 31% Black, and 20% Hispanic. Plasma HIV-1 RNA was <50 copies/mL in 83% and median CD4 T count was 602 cells/ μ L. Abnormal anal cytology was detected in 62%, with corresponding HSIL on biopsy (bHSIL) in 33%. Anal HPV 6, 11, 16 and 18 were detected in 25%, 13%, 32%, and 18% of participants respectively. Prevalence of 0, 1, 2, 3, and 4 qHPV types was 40%, 38%, 17%, 4%, and 1%, respectively. Oral infection with 1 qHPV type was detected in 10% of participants. Study procedures were generally acceptable.

Conclusions—At study baseline, there was a high prevalence of abnormal anal cytology, bHSIL, and HPV infection. Sixty percent of participants had anal infection with preventable qHPV types.

Keywords

anal; human papillomavirus (HPV); human immunodeficiency virus (HIV); dysplasia; vaccine

Introduction

Anal cancer is strongly associated with high-risk (HR) human papillomavirus (HPV) infection and is a common non AIDS-defining cancer in HIV-infected individuals, despite the widespread use of combined antiretroviral therapy (CART).(1–3) The standard treatment for invasive anal cancer is a combination of chemotherapy and radiation therapy which is associated with significant immediate and delayed morbidity.(4) A recent meta-analysis of HIV-infected men in the CART era detected a pooled anal cancer rate of 45.9 per 100,000 (95% Confidence Interval (CI): 31.2–60.3)(5) with HPV 16 the most frequently detected HR-HPV type (35.4% (95% CI 32.9–37.9)). The anal cancer rate in HIV-infected women is estimated to be 30 per 100,000 in the United States (US).(6)

Current anal cancer prevention strategies use exfoliative cytology and high resolution anoscopy (HRA) to diagnose anal high-grade squamous intraepithelial lesions by biopsy (bHSIL), which is then treated to prevent progression to anal cancer. Comprehensive information on the prevalence of any grade of anal SIL in the general population is not currently available. However, in HIV-infected men who have sex with men (MSM), and HIV-infected women the rates of any anal cytological abnormality in recent studies are 47.5% and 39%, respectively.(7, 8)

The quadrivalent HPV vaccine (qHPV) (Gardasil[®], Merck and Co., Kenilworth, NJ) that targets HPV types 6, 11 (low-risk (LR) HPV) and 16, 18 (HR-HPV) is licensed for the prevention of HPV associated anal dysplasia and cancer in both men and women aged 9–26 years. In the licensure study of 4065 men aged 16–26 years, qHPV was shown to prevent 85.6% (97.5% CI, 73.4 to 92.9) of persistent qHPV type anal infections in the per protocol analysis of a subset of 602 MSM.(9) The qHPV prevents HSIL, the precursor lesion of anal cancer, by preventing persistent infection with HR-HPV types 16 and 18 and is both safe and

immunogenic in HIV-infected men and women.(10–12) More recently, a 9-valent vaccine (9vHPV) (Gardasil®9, Merck and Co., Kenilworth, NJ) comprising qHPV and 5 additional HR-HPV types (31, 33, 45, 52, and 58) has been approved by the US Food and Drug Administration (FDA).

Oral HPV infection is also more common in HIV-infected than uninfected individuals with reported prevalence rates of 45% in MSM (8% with HPV 16) and 35% in women (5.4% with HPV 16).(13) Similar to the anogenital site, HR-HPV can also cause certain types of oropharyngeal cancer, also with rates higher in HIV-infected individuals than in the general population.(14) A cross-sectional analysis of women exiting a randomized trial of the bivalent (types 16 and 18) HPV vaccine (Cervarix®, GlaxoSmithKline, Brentford, UK) suggested vaccine efficacy against oral HPV infection.(15) However, none of the HPV vaccines have an FDA indication for the prevention of HPV-associated oropharyngeal cancer.

The quadrivalent vaccine does not have a US FDA indication for men or women over the age of 26 years, and no US guidelines recommend vaccination in this group. All previous licensure studies of qHPV were performed in men and women with low exposure to HPV based on reports of lifetime number of sexual partners, serological evidence of past HPV infection, and a lower prevalence of HPV and HPV-associated disease.(9, 16, 17) These trials demonstrated high efficacy for prevention of HPV associated disease, but little or no effect on prevalent HPV infection.

In order to evaluate the potential effect of the quadrivalent vaccine on HIV-infected individuals over age 26 years, a randomized placebo controlled Phase III study of qHPV was conducted. The study aimed to quantify baseline anal, oral and vaginal HPV infection and to report the effect of vaccinating this HIV-1 infected population who were at high-risk of prior HPV infection to prevent newly acquired persistent infection with qHPV types. Here we present the baseline information evaluating the prevalence of HPV types and of anal bHSIL in this population.

Materials and Methods

Approval was obtained from the AIDS Clinical Trials Group (ACTG) Scientific Agenda Steering Committee, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS, and institutional review board or ethics committees at each participating clinical research site. Written informed consent was obtained from each study participant. (ClinicalTrials.gov number NCT01461096).

This multicenter, randomized, double-blinded, placebo-controlled, Phase III study was opened at selected ACTG sites (N=24, 23 domestic US sites with 540 participants and one site in Brazil with 35 participants) with anal cancer screening programs that included capacity for anal cytology, HRA, and ready access to minimally invasive treatments for HSIL such as topical application of trichloroacetic acid or infrared coagulation. Site clinicians were required to have HRA certification by the AIDS Malignancy Consortium or A5298 study team. The A5298 process included review of training and experience with

HRA, and a log of 50 consecutive HRAs that was reviewed by the study team. Satisfactory logs were defined by having adequate lesion descriptions and detection rates of bHSIL. Site clinicians with satisfactory logs underwent a virtual or in-person site visit to assess at least 4 HRA procedures prior to approval.

Participants were enrolled in two phases, men (target of 464) started enrollment in March 2012 and following a protocol version change; women (target of 100) were enrolled from January 2013 with full enrollment of 575 participants completed in August 2013. Both HIV-infected men and women aged 27 years or older in good general health without a history of invasive or microinvasive cancer at any anal, genital, or oral site were eligible to screen. Men had to report receptive anal sex (defined as a history of receptive penile-anal sex with another man and/or receptive oral-anal sex) within one year prior to entry. Women were required to be on a reliable form of contraception and neither pregnant nor breastfeeding. At least 30% or 140 men were required to have bHSIL as were 50% or 50 of the women to ensure adequate power for the secondary objective of the study assessing the effect of qHPV following treatment of bHSIL.

Following informed consent, at the screening visit participants had anal and vaginal (in females) swabs (Digene Female Swab Specimen Collection Kit (Catalog Number: 5123–1220); Qiagen, Valencia, CA) taken for HPV DNA, an anal cytology swab, a detailed oral examination, and a Scope[®] (Proctor and Gamble, Cincinnati, OH) oral rinse for HPV DNA. (18) A certified HRA provider performed the screening HRA within 45 days prior to entry with biopsies of lesions suspicious for either HSIL, low-grade SIL (LSIL) or condyloma. Individuals with current invasive or microinvasive cancer were not eligible. Potential participants were excluded if they had used topical treatments (trichloroacetic acid, podophyllin, imiquimod or similar compounds, topical 5-fluorouracil, sinecatechins, and cidofovir) within 6 months prior to entry. Additional exclusion criteria included surgical treatment for intra or perianal SIL or condyloma within 6 months prior to entry, prior receipt of one or more doses of a HPV vaccine, bleeding diathesis, or use of any systemic antineoplastic or immunomodulatory treatments within 45 days prior to study entry. For women, a gynecologic examination (including exfoliative cervical cytology screening with or without colposcopy) was also required within 45 days prior to entry.

At a separate enrollment visit participants had an anal HPV swab, vaginal HPV swab (females), collection of serum for HPV antibodies, an oral exam, Scope[®] (Procter and Gamble, Cincinnati, OH) oral rinse, and a whole saliva sample taken for HPV antibodies (specimens stored). These tests were performed 7 days after the screening HPV DNA tests and 14 days after any anal, cervical, vulvar, vaginal, or oral biopsy. Participants were also asked to complete questionnaires addressing the acceptability of all study procedures.

Pathology/cytology

All cytology and anal pathology was evaluated locally in College of American Pathologists (CAP) accredited cytology/pathology laboratories in the US, by local standard of care in Brazil, and reported in accordance with the Bethesda 2001 system terminology guidelines. (19)

HPV detection

HPV serological testing was performed using competitive Luminex immunoassay (HPV-4 cLIA; Merck Research Laboratories, Boston, MA). Anal, cervical and oral HPV DNA polymerase chain reaction (PCR) testing was performed using L1 consensus primers MY09/MY11/HMB01 and B-globin primers PC04/GH20.(20) Specimen adequacy was determined by dot blot hybridization and probed with biotin-labeled B-globin and generic HPV probes; B-globin/HPV-positive samples were then genotyped by using a liquid bead microarray assay (LBMA) based on Luminex technology as described elsewhere.(21) The LBMA typing test is a semi-quantitative assay used to detect 37 HPV types that include 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–56, 58, 59, 61, 62, 64, 66–73, 81–84, is39 and cp6108.

Statistical analysis

Descriptive statistics were used to summarize the study population demographics and the prevalence of abnormal anal cytology, HSIL, and HPV infection. The Wilcoxon rank-sum test was used to compare the differences in absolute CD4 and nadir CD4 T cell counts by bHSIL and by gender. The chi-square test was used to assess the association between HPV infection and HSIL status (with no adjustment for coinfections) and between HPV infection and sex at birth. The differences in experience and acceptability of the HRA procedure between men and women were assessed via the Wilcoxon rank-sum test. All statistical tests were performed at the 0.05 level without adjustment for multiple comparisons.

Results

Out of 738 participants screened, 575 were enrolled and randomized between March 2012 and August 2013. (Figure 1) Four hundred and seventy-two (82%) were male and 103 (18%) were female with a median age of 47 years (interquartile range (IQR) 41–53 years). Forty-six percent were white non-Hispanic, 31% were black non-Hispanic, 20% were Hispanic, and 3% were Asian, Pacific Islander, American Indian, Alaskan, or ‘more than one race’. The majority (53%) of males were white non-Hispanic, and most females (56%) were black non-Hispanic. (Table 1)

Ninety-eight percent of participants were receiving CART at study entry and the median duration on antiretroviral drugs was 4.9 years (IQR 2.4, 9.9). HIV RNA was suppressed at less than 50 copies per mL in plasma in 470 (83%) of participants. The median and nadir absolute CD4 T cell counts were 602 cells/ μ L (IQR 436–767) and 255 cells/ μ L (IQR 110–403), respectively. At study entry 33% had bHSIL. Participants with bHSIL had a lower median absolute and nadir CD4 T cell count, and were less likely to have HIV RNA <50 copies per mL compared to the no bHSIL group (542 versus 629 cell/ μ L, $p=0.009$, 203 versus 273 cells/ μ L, $p=0.002$, and 143 (79%) versus 327 (85%), respectively). (Table 1) Anal cytology results were available in 572/575 (99.0%) participants. Abnormal anal cytology was detected in 357 (62%) participants, and was more frequent in participants with bHSIL (83% vs. 52%) (Table 2).

Anal HPV infection with qHPV types was common in this population with 346/574 (60%) having detectable infection. There was no significant differences in the prevalence or

number of HPV types identified, or in qHPV or 9vHPV types, between men and women. (Table 3) The most common HPV type detected was HPV 16 (32%), followed by HPV 6 (25%), HPV 18 (18%) and HPV 11 (13%). (Table 4) The prevalence of 1, 2, 3, and 4 qHPV types was 38%, 17%, 4%, and 1% respectively. When the additional 5 HR-HPV types of the 9vHPV were considered, 83% of participants had at least one type detected, with prevalence of HR-HPV types 31, 33, 45, 52 and 58 ranging from 13% to 25%. Each of the HR-HPV types in the 9vHPV was significantly associated with the presence of HSIL on biopsy (p-values <.05) and 95% of participants with bHSIL had 1 or more 9vHPV types detected. We investigated the relationship of bHSIL and non-vaccine HR-HPV types (35, 39, 51, 56, 59, 66, 68). We found that types 39, 56, and 68 were also significantly associated with the presence of bHSIL (p<.05). (Data not shown). Human papillomavirus types 6 and 11 (LR-HPV) were not associated with HSIL. (Table 4) The prevalence of HSIL was linearly associated with number of HR-HPV types detected from over 20% with one HR-HPV to over 60% with 7 or more HR-HPV types, $P<.001$ by Chi-square test. (See supplemental Figure 1). Demographic and HIV surrogate marker information were not related to the presence of the 7 HR-HPV types. (Data not shown)

Oral HPV infection with any qHPV type was present in 10% of participants, and 20% with any 9vHPV types. There were 14 (2%), 13 (2%), 27 (5%) and 14 (2%) participants infected with HPV-6, 11, 16 and 18, respectively. Of the 575, 52 (9%) had one qHPV type infection and 8 (1%) had two types. (Supplemental Table)

Vaginal HPV infection with any qHPV type was present in 44% of females. There were 9 (9%), 7 (7%), 24 (23%) and 16 (16%) participants infected with HPV-6, 11, 16 and 18 respectively. Of the 103, 34 (33%) had one qHPV type infection and 11 (11%) had two types. (Supplemental Table)

The kappa (k) statistic was used to assess concordance of the HPV types observed in the anal, oral, and vaginal samples. There was only slight agreement of qHPV or 9vHPV types observed in the anal and oral samples in men and women ($k < 0.2$). Between the anal and vaginal sites in women, there was fair to moderate ($k = 0.37$) concordance of qHPV types and fair but not high ($k = 0.24$) concordance of 9vHPV types. The concordance of qHPV and 9vHPV types observed in the vaginal and oral samples in women was fair ($k = 0.21$), and similar for 9vHPV.

Serology for HPV types was performed at baseline. In both male and female participants, serology was positive indicating previous infection with qHPV types 6, 11, 16 and 18 in 62.5%, 41.5%, 47.5%, and 32.0% respectively. (Data not shown)

Approximately 50% of participants experienced their first HRA in the context of this trial including 50% of men and 71% of women. There was no difference in HRA acceptability between the sexes ($P=0.24$). (Supplemental Table) The majority (median >80%) of all participants tolerated all procedures and would be very likely (median >70%) to recommend anal cancer screening to others. (Data not shown)

Discussion

In this unvaccinated population of men and women over 26 years of age with predominantly well controlled HIV infection on CART, abnormal anal cytology and anal HPV infection was highly prevalent, with detection of HR-HPV vaccine types significantly correlated with detection of HSIL on anal biopsy.

HPV prevalence rates were higher than those found in previous observational studies and may be related to several factors including; optimization of sampling at two distinct time points from each anatomical site with data pooling, a median participant age of 47 years, and high prevalence of HPV antibodies indicating high levels of prior sexual HPV exposure and infection. Additionally, although HPV detection may be transient in the anal canal it is likely that there was ongoing sexual exposure and infection at the time of screening. Human papillomavirus type 16 was the most common type detected in this and other studies, although at a lower level in men than in a previous meta-analysis.(5, 22) Despite the high HPV prevalence it was initially encouraging that only 5 participants had all 4 qHPVs detected in the anal canal, and had the theoretical potential for some degree of protection with the vaccine. One participant had all 9vHPV types detected.

The connection between immunosuppression, and HPV associated squamous cell carcinomas has been established in HIV-infected individuals, particularly with CD4 T cells <200 cells/mm³.(23, 24) In our study, a low nadir CD4 count was associated with the presence of bHSIL lending support to the opinion that once HPV infection is established, the effect of immune reconstitution on HPV clearance is minimal. Most participants in our study were virologically suppressed, but lower rates of current suppression were seen in those individuals with bHSIL. There is accumulating evidence that virological suppression may be important in the control of HPV related disease and that the cumulative viral load, a measure of longer term HIV exposure, may be associated with an increased incidence of anal cancer. (25) This is supported by the observation that early initiation of antiretroviral therapy, which is now widely recommended, is associated with a reduced risk of virally mediated cancers. (26)

Abnormal anal cytology was highly prevalent, with atypical squamous cells of undetermined significance (ASCUS) and LSIL comprising the majority of cytological abnormalities. We observed a sensitivity and specificity of abnormal anal cytology for bHSIL of 83% and 47%, respectively. Although this study utilized a non-commercial PCR-based HPV detection test which is not currently approved by the FDA, pairing anal cytology with FDA approved, commercially available HR HPV testing may improve test characteristics similar to current cervical cytology screening algorithms. It is of interest that the number of HR-HPV vaccine types detected was significantly associated with bHSIL at the time of HRA. It may be feasible to use HR-HPV testing as the initial screening test to determine who should proceed to HRA, especially when using HPV tests with typing information that includes non-9vHPV HR types also associated with cytological abnormalities and bHSIL.

The study limitations in part relate to the pre-stipulated requirements for 50% of female participants to have bHSIL, and following full accrual of the non-bHSIL group 15 female

participants were excluded without bHSIL. For men, it was required that 30% have bHSIL, but no male participants were excluded for this reason. This prevents estimation of HSIL prevalence in HIV-infected women. However, this limitation does not affect predictors of HSIL. We did not require a minimum number of anal biopsies, or random biopsies if no visible HSIL was detected as has been done in some studies, so despite provider certification in the HRA procedure, HSIL may have been missed at baseline. Furthermore, a central pathology review was not utilized to verify local anal pathology diagnoses, although all sites except Brazil had CAP accreditation, and we did not type HSIL histology specimens to determine the associated HPV type.

Despite the established increased risk of anal cancer in both HIV-infected men and women, (6) there are a limited number of centers with expertise in screening, diagnosis and minimally invasive treatment of HSIL. This study demonstrates that even in a cohort enriched with individuals with a higher prevalence of HR HPV infection, detection of HR HPV increases the risk for detecting prevalent bHSIL. Future studies should evaluate the role of HPV testing, especially those providing typing information in anal cancer screening algorithms to focus HRA on those at highest risk. Primary prevention with the 9vHPV vaccine vaccine is critical for preventing anal HSIL and cancer, especially in areas where anal cancer screening services are limited and in areas with high HIV incidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

In both HIV-infected men and women aged over 26 years there was a high prevalence of abnormal anal cytology, high-grade anal dysplasia, and quadrivalent vaccine-type HPV infection

Figure 1.
Study Consort Flow Diagram

Table 1

Baseline Characteristics of Study Participants, by bHSIL and gender

Characteristic		Total (N=575)	bHSIL at study entry		P-Value	Male (N=472)	Female (N=103)	P-Value
			bHSIL (N=187)	No bHSIL (N=388)				
Age at study entry	N	575	187	388	0.808 *	472	103	0.026 *
	Median	47	47	47		47	48	
	Q1, Q3	41, 53	41, 53	41, 53		40, 52	42, 55	
Race/ethnicity	White Non-Hispanic	262 (46%)	73 (39%)	189 (49%)	0.120 **	249 (53%)	13 (13%)	<.001 **
	Black Non-Hispanic	179 (31%)	61 (33%)	118 (30%)		121 (26%)	58 (56%)	
	Hispanic (Regardless of Race)	117 (20%)	49 (26%)	68 (18%)		85 (18%)	32 (31%)	
	Asian, Pacific Islander	12 (2%)	3 (2%)	9 (2%)		12 (3%)	0 (0%)	
	American Indian, Alaskan Native	2 (0%)	0 (0%)	2 (1%)		2 (0%)	0 (0%)	
	More than one race	3 (1%)	1 (1%)	2 (1%)		3 (1%)	0 (0%)	
IV drug history	Previously	46 (8%)	18 (10%)	28 (7%)		33 (7%)	13 (13%)	0.056 **
HIV RNA (copies/mL)	<50	470 (83%)	143 (79%)	327 (85%)	0.022 **	398 (85%)	72 (76%)	0.077 **
	Missing	11	6	5		3	8	
Lowest documented CD4 count	N	515	169	346	0.002 *	434	81	<.001 *
	Min, Max	0, 1,272	3, 1,272	0, 854		0, 1,272	1, 865	
	Median	255	203	273		273	179	
	Q1, Q3	110, 403	66, 356	135, 419		131, 416	35, 283	
Absolute CD4 count	N	569	183	386	0.009 *	468	101	0.380 *
	Min, Max	66, 1,697	66, 1,617	78, 1,697		66, 1,697	66, 1,617	
	Median	602	542	630		599	623	
	Q1, Q3	436, 767	389, 727	458, 801		437, 767	432, 801	

* Wilcoxon Test

** Chi-Square Test

bHSIL: high-grade squamous intraepithelial lesion on anal biopsy, IV: intravenous

Table 2

Baseline Cytology Results, by HSIL and by Sex

Type	bHSIL at study entry				Sex	
	Total (N=570)	bHSIL (N=186)	No bHSIL (N=384)		Male (N=468)	Female (N=102)
Overall	570 (100%)	186 (100%)	384 (100%)		468 (100%)	102 (100%)
Normal	213 (37%)	30 (16%)	183 (48%)		187 (40%)	26 (25%)
Normal	199	29	170		174	25
Other abnormality [#]	14	1	13		13	1
Abnormal	357 (63%)	156 (84%)	201 (52%)		281 (60%)	76 (75%)
ASCUS	181	60	121		134	47
ASC-H	12	8	4		8	4
LSIL	126	57	69		109	17
HSIL	33	27	6		26	7
HSIL: features of invasion	1	1	0		1	0
Other abnormality	4	3	1		3	1

bHSIL: high grade squamous intraepithelial lesion on anal biopsy, ASCUS: Atypical squamous cells of undetermined significance, LSIL: low grade squamous intraepithelial lesions, HSIL: high-grade squamous intraepithelial lesion

5 participants had unspecified or missing results

[#] Abnormalities presented in supplemental Table 4S

Table 3

Baseline Anal HPV Types, by bHSIL and Sex

Characteristic	bHSIL at study entry				Sex	
	Total (N=574)	bHSIL (N=187)	No bHSIL (N=387)	P-Value*	Male (N=471)	Female (N=103)
Number of HPV infections (vaccine types)						
0	228 (40%)	51 (27%)	177 (46%)	<.001	181 (38%)	47 (46%)
1	220 (38%)	81 (43%)	139 (36%)		179 (38%)	41 (40%)
2	98 (17%)	44 (24%)	54 (14%)		86 (18%)	12 (12%)
3	23 (4%)	8 (4%)	15 (4%)		20 (4%)	3 (3%)
4	5 (1%)	3 (2%)	2 (1%)		5 (1%)	0 (0%)
HPV infection risk (of qHPV vaccine type)						
None	228 (40%)	51 (27%)	177 (46%)	<.001	181 (38%)	47 (46%)
Low risk only	103 (18%)	30 (16%)	73 (19%)		87 (18%)	16 (16%)
Any high risk	243 (42%)	106 (57%)	137 (35%)		203 (43%)	40 (39%)
Yes	346 (60%)	136 (73%)	210 (54%)	<.001	290 (62%)	56 (54%)
No	228 (40%)	51 (27%)	177 (46%)		181 (38%)	47 (46%)
Any HPV (6/11/16/18)						
Yes	361 (63%)	149 (80%)	212 (55%)	<.001	293 (62%)	68 (66%)
No	213 (37%)	38 (20%)	175 (45%)		178 (38%)	35 (34%)
Any HPV (31/33/45/52/58)						
Yes	476 (83%)	177 (95%)	299 (77%)	<.001	394 (84%)	82 (80%)
No	98 (17%)	10 (5%)	88 (23%)		77 (16%)	21 (20%)

* Chi-Square Test

bHSIL: high-grade squamous intraepithelial lesion on anal biopsy, HPV: human papillomavirus, qHPV: quadrivalent HPV vaccine One participant had insufficient material on swab.

Low-risk HPV only: 6 or 11, without 16 or 18.

Any high-risk HPV: 16 or 18 present, regardless of other types.

Table 4

Baseline Anal bHSIL Prevalence by HPV Type

HPV type	Overall HPV prevalence	bHSIL prevalence, HPV type detected	bHSIL prevalence, HPV type not detected	Prevalence Ratio	P-Value
HPV 6	141 (25%)	45/141 (31.9%)	142/433 (32.8%)	0.97	0.847
HPV 11	76 (13%)	30/76 (39.5%)	157/498 (31.5%)	1.25	0.169
HPV 16	498 (87%)	82/184 (44.6%)	105/390 (26.9%)	1.66	<.001
HPV 18	104 (18%)	48/104 (46.2%)	139/470 (29.6%)	1.56	0.001
HPV 31	126 (22%)	55/126 (43.7%)	132/448 (29.5%)	1.48	0.003
HPV 33	97 (17%)	42/97 (43.3%)	145/477 (30.4%)	1.42	0.013
HPV 45	72 (13%)	41/72 (56.9%)	146/502 (29.1%)	1.96	<.001
HPV 52	137 (24%)	55/137 (40.1%)	132/437 (30.2%)	1.33	0.030
HPV 58	145 (25%)	64/145 (44.1%)	123/429 (28.7%)	1.54	<.001

bHSIL: high-grade squamous intraepithelial lesion on anal biopsy, HPV: human papillomavirus