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Cutaneous human papillomavirus types detected on the surface of male external genital lesions: A case series within the *HPV Infection in Men Study*

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Abstract

Background—Cutaneous human papillomaviruses (HPVs) may be associated with cutaneous epithelial lesions and non-melanoma skin cancers. No study has systematically evaluated the presence of genus beta [β]-HPV in male genital skin or external genital lesions (EGLs).

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Objectives—To examine cutaneous β-HPV types detected on the surface of EGLs in men and describe their presence prior to EGL development.

Study design—A retrospective case series was conducted among 69 men with pathologically confirmed EGLs (n=72) who participated in the *HPV Infection in Men Study*. Archived exfoliated cells collected from the surface of each EGL and normal genital skin specimens 6–12 months preceding EGL development were tested for β-HPV DNA using a type-specific multiplex genotyping assay.

Results—β-HPV DNA was detected on 61.1% of all EGLs, with types 38 (16.7%), 5 (15.3%), and 12 (12.5%) most commonly identified. HPV prevalence differed across pathological diagnoses, with the largest number of β-HPV types detected on condylomas. Most β-HPV types were detected on normal genital skin prior to EGL development, though the prevalence was lower on EGLs compared to preceding normal genital skin.

Conclusions—EGLs and the normal genital skin of men harbor a large number of β-HPV types; however, it appears that β-HPVs are unrelated to EGL development in men. Despite evidence to support a causal role in skin carcinogenesis at UVR-exposed sites, cutaneous HPV appears unlikely to cause disease at the UVR-unexposed genitals.

Background

Human papillomaviruses (HPV) cause substantial disease in men, including non-cancerous and cancerous lesions of the external genitalia.[1, 2] Condyloma, or genital warts, is a common clinical manifestation of non-oncogenic genital HPV infection.[3] These benign epithelial lesions are highly infectious[3] and occur most frequently among men 25–29 years of age.[4] We and others have consistently shown that non-oncogenic mucosal HPV types 6/11 are detected in 75–100% of condylomas,[5-9] and that half are co-infected with oncogenic mucosal HPV types, particularly HPV 16.[7, 8] Penile intraepithelial neoplasia (PeIN) is a presumed precursor lesion to HPV-related penile cancer. Though rarer than cervical intraepithelial neoplasia (CIN), PeIN shares histologic similarities with CIN, presenting as low, moderate, or severe dysplasia.[10] The progression of PeIN from low- to high-grade lesions is thought to be rare, though the proportion that progress to penile cancer remains unknown. Approximately 70–100% of PeIN have tested positive for mucosal HPV,[11] with HPV 16 being the most common;[1] however, mucosal HPV is detected in only half of penile carcinomas.[11, 12]

Most studies examining the role of HPV in the development of male external genital lesions (EGLs) have evaluated mucosal HPV types of genus alpha (α-HPV);[5, 8, 9, 13-15] however, recent data suggest that cutaneous HPV types may also have oncogenic potential.[16, 17] A subset of cutaneous HPV types in genus beta (β-HPV) have been implicated in non-melanoma skin cancers.[16] It has been hypothesized that skin infected with β-HPV demonstrates increased susceptibility to ultraviolet radiation (UVR)-induced DNA damage, ultimately leading to skin carcinogenesis.[17] However, little is known about the role of β-HPV types in skin carcinogenesis at UVR-unexposed anatomic sites, such as the genitals.

Objectives

The purpose of this study was to examine the distribution of cutaneous β-HPV types detected on the surface of male EGLs and describe the natural history of these infections up to 12 months prior to lesion detection.

Study design

A retrospective case series was nested within the *HPV Infection in Men (HIM) Study*, an ongoing prospective study of the natural history of HPV infections among men living in the United States (US; Tampa), Brazil (São Paulo), and Mexico (Cuernavaca). The *HIM Study* cohort consists of >4,000 men aged 18–70 years who were recruited between 2005 and 2009, reported no prior diagnosis of anogenital cancer or genital warts and no current symptoms of or treatment for a sexually transmitted infection, including HIV/AIDS. Participants were examined approximately every six months for up to four years. Additional details of the *HIM Study* are published elsewhere.[18, 19]

Participants were included in the current analysis if they developed an incident EGL that was detected at a follow-up visit and was pathologically confirmed between February 2009 (when lesion biopsy began in the *HIM Study*) and May 2011 (Figure 1). Participants provided written informed consent, and the human subjects committees of participating institutions approved all procedures.

Specimen collection and processing

At each visit, participants completed a risk factor questionnaire and underwent a clinical examination. Visual inspection of the external genital skin was conducted and exfoliated cells were collected from the normal genital skin. Using Dacron swabs prewetted with sterile saline, the penile head, penile shaft, and scrotum were sampled, combined into one specimen, and archived.[19] If an EGL was identified, exfoliated cells from the surface of the lesion were collected prior to the normal genital skin sampling and archived separately.

Visually distinct EGLs were biopsied and subjected to pathological evaluation. Formalin-fixed paraffin-embedded (FFPE) tissue blocks were processed in the US (tissue blocks from Brazil and Mexico were shipped to the US). Fifteen 4-micron paraffin sections were cut from each block. Briefly, the two outer sections were discarded, four sections were used to prepare two separate slides, and an additional nine sections were collected in an Eppendorf tube for DNA retrieval. Slides were stained with hematoxylin and eosin and were evaluated by two independent pathologists for the presence of inflammatory, infectious, pre-neoplastic, or neoplastic conditions. A pathology panel was convened to provide final adjudication for discordant interpretations and quality control for 10% of all specimens.

DNA extraction and HPV genotyping

All genital swab specimens underwent DNA extraction using the QIAamp Media MDx Kit (Qiagen, Gaithersburg, MD). Specimens were tested for the presence of mucosal HPV by PCR and genotyped using Linear Array (Roche Molecular Diagnostics, Alameda, CA),[20, 21] which detects 37 α-HPV types including 6, 11, 16, and 18.[22] Archived surface of EGL specimens and normal genital skin specimens from two visits prior to lesion detection (six and 12 months prior) were also tested for the presence of β-HPV using a type-specific multiplex genotyping (TS-MPG) assay (IARC, Lyon, France), which combines multiplex PC[23-25] with a bead-based Luminex technology.[26, 27] The TS-MPG assay detects 25 β-HPV types (species β1: HPV types 5, 8, 12, 14, 19, 20, 21, 24, 25, 36, 47, 93; species β2: HPV types 9, 15, 17, 22, 23, 37, 38, 80; species β3: HPV types 49, 75, 76; species β4: HPV 92; species β5: HPV 96). Two primers for the amplification of β-globin were added to provide a positive control for the quality of template DNA.[28]

Statistical analysis

Pathological diagnoses of EGLs were categorized as condyloma, probable condyloma, PeIN, and other. Probable condylomas included those suggestive but not diagnostic of HPV or

condyloma, such as benign squamous keratosis. Other EGLs included various HPV-unrelated skin conditions, such as seborrheic keratosis and skin tags. PeIN included grades I–III.

Among newly detected, pathologically confirmed, and pathologically distinct EGLs, β-HPV prevalence was estimated for grouped (any β-HPV type and species-specific types) and genotype-specific infections. The classification of any β-HPV type was defined as a positive test result for ≥1 of the 25 β-HPV genotypes listed above. Prevalence estimates were stratified by EGL pathology and examined among lesions that tested negative or positive for common causative mucosal α-HPV types (6, 11, 16, 18), with groups compared using the Monte Carlo estimation of exact Pearson chi-square tests. Additional analyses were conducted to examine whether β-HPV DNA-positive lesions also had β-HPV DNA of the same genotype detected on the normal genital skin 6-12 months prior to lesion detection. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

As of May 2011, 192 men had developed incident, pathologically confirmed EGLs within the *HIM Study* (Figure 1). Of these, 72 men had available archived specimens from the surface of lesions and normal genital skin specimens prior to lesion detection, both of which were evaluated for the presence of β-HPV DNA. With respect to baseline sociodemographic characteristics, men with available specimens were comparable to men with unavailable specimens. Three lesions from three men had inadequate specimens for β-HPV genotyping.

The final case series included 69 men who were the first to have developed incident EGLs (n=72) confirmed by pathology (Table 1). At biopsy, men ranged in age from 20 to 60 years with a median of 31 years. Half of men (50.7%) were white, half (47.0%) were single or never married, one-third (34.9%) had some college education, and one-fourth (25.8%) reported being current smokers. A large proportion of men (43.9%) reported having ≥20 lifetime female sex partners, and 10.6% reported having ≥1 recent male anal sex partner. Among the 72 distinct EGLs detected, 28 were condyloma, 18 were probable condyloma, six were PeIN, and 20 were other HPV-unrelated diagnoses.

Overall, 44 EGLs (61.1%) tested DNA-positive for one or more β-HPV types (Table 2). Twenty-two different β-HPV types were detected, with HPV 38 (n=12; 16.7%) being the most common, followed by HPV 5 (n=11; 15.3%), HPV 12 (n=9; 12.5%), and HPV 17 (n=8; 11.1%). Genotype diversity and distribution varied by country, with Brazil having the highest overall prevalence (Brazil: 80.0%; Mexico: 60.0%; US: 44.4%) and Mexico having the least number of types (data not shown). Multiple infections were common, with 27 β-HPV DNA-positive EGLs (61.4%) containing >2 types.

The greatest β-HPV prevalence and type diversity were observed among condylomas (Table 2), with 22 (78.6%) containing β-HPV DNA. Of the 18 types detected, HPV 5 and 38 (n=6; 21.4% each) were the most common, followed by HPV 8 and 14 (n=5; 17.9% each). Only six (33.3%) of the 18 probable condylomas were β-HPV DNA-positive. Among six cases of PeIN, two (33.3%) were β-HPV DNA-positive. Five types were detected on PeIN, with HPV 21 (n=2; 33.3%) being the most common.

To assess whether the presence of known causative α-HPV types was associated with β-HPV detection, β-HPV prevalence was further stratified by pathological diagnosis and presence of α-HPV types 6/11 or 16/18. Few cases of condyloma (n=6; 21.4%) were negative for both α-HPV 6 and 11 (Table 3). β-HPV prevalence was highest among α-HPV 6/11 DNA-positive condylomas for all types except β-HPV 21, 38, 80, and 96, which had a

higher prevalence in α-HPV 6/11 DNA-negative condylomas. Half of PeIN (n=3; 50.0%) were negative for both α-HPV 16 and 18. A greater number of β-HPV types were present among α-HPV 16/18 DNA-positive PeIN. β-HPV 17 was present in HPV 16/18 DNA-negative PeIN (n=1; 33.3%) but was absent in all HPV 16/18 DNA-positive PeIN.

β-HPVs were repeatedly detected 6–12 months prior to EGL development (Table 4). For all EGLs that tested positive for β-HPV types 15, 36, 37, 75, or 92, DNA of the same genotype was detected on normal genital skin 6–12 months prior to lesion development. Lesions positive for β-HPV types 38 (91.7%), 5 (81.8%), and 23, 24, and 96 (80.0% each) also demonstrated high levels of detection prior to lesion development. Similar trends were seen among condyloma and PeIN (data not shown). Generally, it was uncommon for β-HPV types to be detected for the first time on the EGL.

To further examine temporality, β-HPV prevalence was compared across study visits (Figure 2). The overall prevalence of β-HPV was substantially lower on the surface of lesions than on preceding normal genital skin, with similar trends seen among condyloma. Similarly, multiple β-HPV types presented less frequently on the surface of lesions than on normal genital skin prior to lesion development.

Discussion

In this case series, we demonstrate that condyloma and the normal genital skin of otherwise healthy men harbor a large number of cutaneous β-HPV types. While most types detected on male EGLs were present on the normal genital skin prior to lesion development, the prevalence of β-HPV was lower among lesions compared to normal genital skin.

Few published studies have examined the presence of cutaneous HPV among male EGLs;[9, 29-31] however, all have used varying methods and have focused on a single lesion type, making comparisons across studies difficult. In two studies examining penile carcinomas,[29, 3031] HPV 8 was detected in all tumors. While our study did not include men with invasive penile carcinoma, we are the first to show that β-HPV was present on 33% of pre-cancerous PeIN, though β-HPV types 5 and 8 were not detected.

According to condyloma surveillance recently conducted in Sweden, 42% of mucosal HPV DNA-negative condylomas were positive for β-HPV types 36, 49, 75, and 80,[9] though the β-HPV prevalence among mucosal HPV DNA-positive condylomas was not reported. In the current study, we found a high prevalence of β-HPV DNA (77–83%), regardless of mucosal HPV 6/11 DNA-status. Among PeIN, the prevalence of β-HPV was 50% for both HPV 16/18 DNA-negative and -positive lesions, though our sample size was limited. Co-infection with mucosal and cutaneous HPV types appears to be common among EGLs, with another study reporting that co-infection with mucosal HPV 16/18 and β-HPV 8 was common among penile carcinomas *in situ*.[31] Altogether, these findings suggest the possibility of multiple viral pathways to disease or perhaps co-transmission of mucosal and cutaneous HPV types during sexual activity.

For most β-HPV DNA-positive lesions examined in this study, DNA of the same genotype was detected on normal genital skin collected prior to lesion detection. Interestingly, the prevalence of β-HPV was substantially lower among lesions than on normal genital skin ≥6 months prior to lesion development. In a cross-sectional study of six benign and malignant cutaneous tumors, similar findings were observed, with β-HPV detected in 33% of tumor tissues and 50% of adjacent normal tissues.[32] In contrast, the prevalence of β-HPV detected in or near cutaneous squamous cell carcinoma tissue has been shown to be considerably higher than in adjacent normal skin,[33] supporting the hypothesis that β-HPV may be

involved in the development of non-melanoma skin cancer. Furthermore, epidemiologic studies conducted among women have shown that the relative frequency of mucosal α-HPV types 16 and 18 (known to cause cervical cancer) increases significantly with increasing lesion severity.[34, 35] As such, we would expect the prevalence of β-HPV to be highest in lesions if the virus was actively involved in EGL development. Given that β-HPVs are commonly detected on normal genital skin, we concur that β-HPVs may simply be part of the commensal microbiome of the cutaneous epithelium.[36]

To our knowledge, this is the first systematic investigation into the role of cutaneous HPV in the development of a variety of male EGLs and the first to report on the simultaneous presence of cutaneous and mucosal HPV types on the surface of both pathologically confirmed lesions and normal genital skin samples collected prior to lesion development. In this study, we employed the highly sensitive TS-MPG assay, which improved our ability to detect a large number of β-HPV infections compared with traditional PCR methods.[37] However, there are limitations that must be considered. First, HPV types detected on the surface of a lesion may not represent those present within biopsy tissue.[38] Moderate to high agreement between sampling methods was found for α-HPV types[39] but remains unknown for β-HPV types. Second, swabbing the surface of a lesion may introduce contamination from the normal genital skin surrounding the EGL; however, this is unlikely given the lower HPV prevalence among EGLs. Third, misclassification of pathological diagnosis may have occurred, though it would have been minimized by the use of a pathology panel. To further evaluate the causal role of cutaneous HPV in the development of male EGLs, studies with a larger sample size and matched controls, in addition to a measure of HPV transcriptional activity, would be needed.

Our findings and those of others have shown that cutaneous β-HPVs are ubiquitous in the general population[24, 33] and may even be commensal organisms. While there is increasing evidence to support a causal role in skin carcinogenesis at UVR-exposed anatomic sites,[26, 40, 41] it appears that cutaneous HPV infection is unlikely to cause malignant or benign disease at UVR-unexposed sites, such as the genitals. The underlying mechanism of cutaneous HPV pathogenesis, and particularly carcinogenesis, remains unclear. Future prospective studies should focus on elucidating the pathways from HPV infection to disease progression and uncover the role of UVR in the disease process.

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Abbreviations

HPV	Human papillomavirus
EGL	external genital lesion
PeIN	penile intraepithelial neoplasia
CIN	cervical intraepithelial neoplasia
US	United States
HIM Study	HPV Infection in Men Study
β-HPV	beta-HPV
α-HPV	alpha-HPV

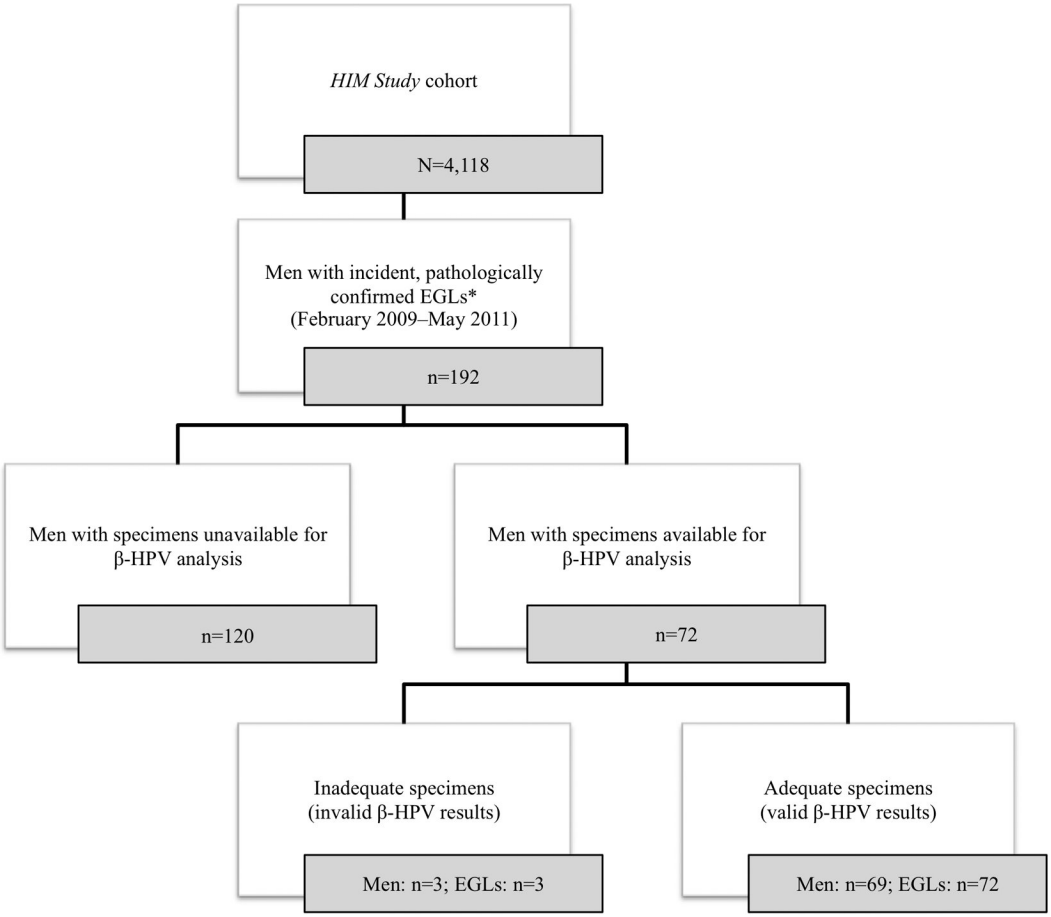

Figure 1.

Numbers of men and newly acquired, pathologically confirmed external genital lesions (EGLs) available for analysis among men enrolled in the *HPV Infection in Men Study*.

*Sample sizes reflect pathologically distinct EGLs, and not necessarily all EGLs detected.

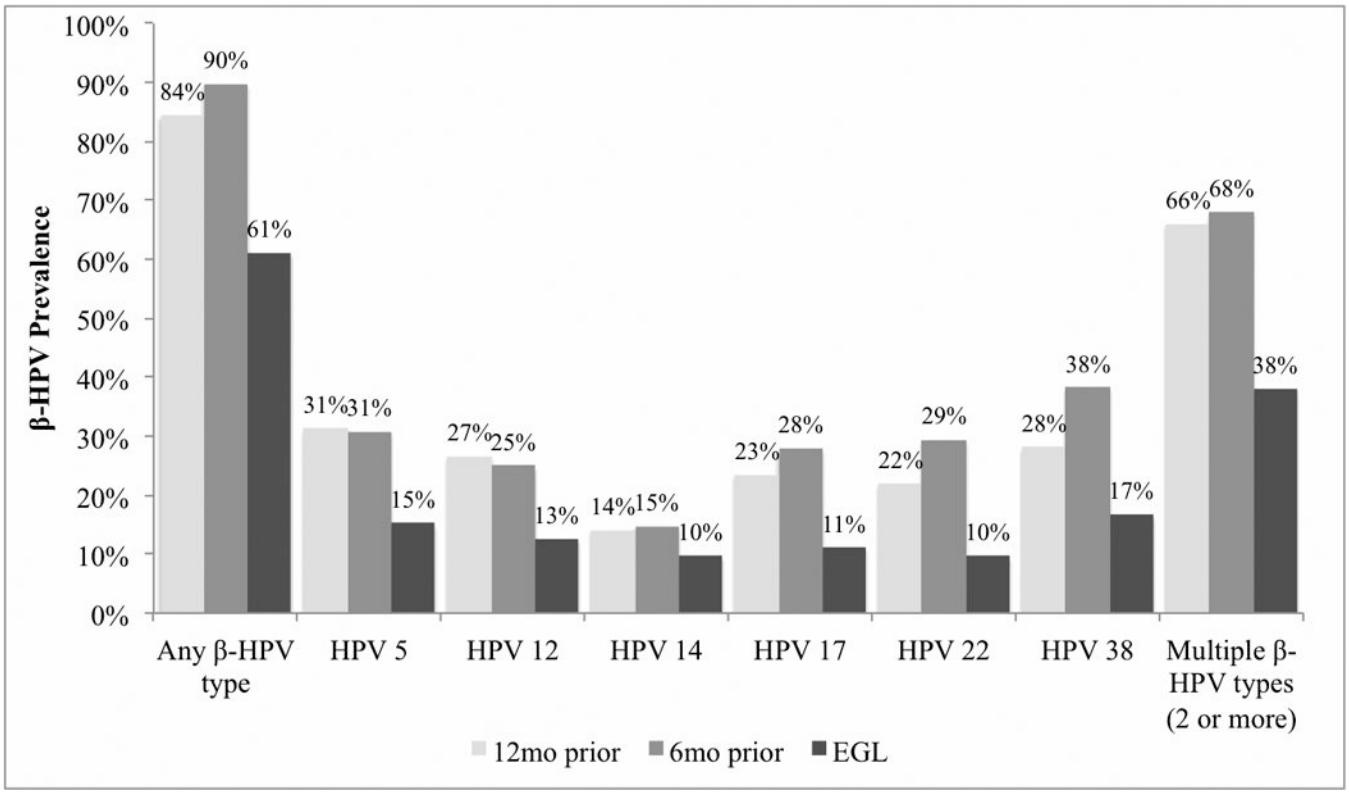

Figure 2.
Beta (β)-HPV prevalence among newly detected, pathologically confirmed external genital lesions (EGLs) (n=72) and among normal genital skin 6 and 12 months prior to lesion detection.

Table 1

Characteristics of 69 Men in the *HPV Infection in Men Study* at the Time of a Newly Detected, Pathologically Confirmed External Genital Lesion

Characteristic	N (%)
Country of residence	
United States	25 (36.2)
Brazil	25 (36.2)
Mexico	19 (27.5)
Age, years	
Median (range)	31.1 (20.1–60.0)
Mean (SD)	32.6 (8.8)
18–30	34 (49.3)
31–44	28 (40.6)
45–73	7 (10.1)
Race	
White	35 (50.7)
Black	15 (21.7)
Asian/Pacific Islander	0 (0)
American Indian/Alaskan Native	0 (0)
Mixed	18 (26.1)
Missing data	1 (1.5)
Marital status	
Single or never married	31 (47.0)
Married	15 (22.7)
Cohabitating	16 (24.2)
Divorced/separated/widowed	4 (6.1)
Education, years	
<12	8 (12.1)
12	15 (22.7)
13–15	23 (34.9)
16	14 (21.2)
≥17	5 (7.6)
Missing data	1 (1.5)
Circumcision	
No	41 (59.4)
Yes	28 (40.6)
Current smoker	
No	49 (74.2)
Yes	17 (25.8)
Sexual orientation	
MSW	58 (84.1)
MSM	4 (5.8)

Characteristic	N (%)
MSWM	4 (5.8)
Missing data	3 (4.3)
Lifetime female sex partners	
0–1	10 (15.2)
2–9	11 (16.7)
10–19	13 (19.7)
20–49	20 (30.3)
≥50	9 (13.6)
Missing data	3 (4.6)
Female sex partners in past 3–6 months	
0	7 (11.1)
1	30 (47.6)
2	9 (14.3)
≥3	16 (25.4)
Missing data	1 (1.6)
Male anal sex partners in past 3 months	
0	59 (89.4)
1	3 (4.6)
2	1 (1.5)
≥3	3 (4.6)

Data are n (%).

MSW: men who have sex with women; MSM: men who have sex with men; MSWM: men who have sex with women and men.

Table 2

Beta (β)-HPV Type Distribution Among Newly Detected, Pathologically Confirmed External Genital Lesions (n=72), by Pathological Diagnosis

		Pathological Diagnosis N (%)			
	Total n=72	Condyloma n=28	Probable condyloma[a] n=18	PeIN n=6	Other[b] n=20
HPV species/type	N (%)	N (%)	N (%)	N (%)	N (%)
Any β-HPV type	44 (61.1)	22 (78.6)	6 (33.3)	2 (33.3)	14 (70.0)
β1					
Any β1	35 (48.6)	18 (64.3)	5 (27.8)	2 (33.3)	10 (50.0)
HPV 5	11 (15.3)	6 (21.4)	1 (5.6)	0 (0)	4 (20.0)
HPV 8	6 (8.3)	5 (17.9)	0 (0)	0 (0)	1 (5.0)
HPV 12	9 (12.5)	3 (10.7)	1 (5.6)	0 (0)	5 (25.0)
HPV 14	7 (9.7)	5 (17.9)	2 (11.1)	0 (0)	0 (0)
HPV 19	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HPV 20	3 (4.2)	0 (0)	2 (11.1)	0 (0)	1 (5.0)
HPV 21	6 (8.3)	2 (7.1)	0 (0)	2 (33.3)	2 (10.0)
HPV 24	5 (6.9)	2 (7.1)	1 (5.6)	0 (0)	2 (10.0)
HPV 25	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HPV 36	5 (6.9)	3 (10.7)	0 (0)	0 (0)	2 (10.0)
HPV 47	4 (5.6)	3 (10.7)	0 (0)	0 (0)	1 (5.0)
HPV 93	1 (1.4)	0 (0)	0 (0)	0 (0)	1 (5.0)
β2					
Any β2	25 (34.7)	13 (46.4)	4 (22.2)	2 (33.3)	6 (30.0)
HPV 9	6 (8.3)	2 (7.1)	0 (0)	1 (16.7)	3 (15.0)
HPV 15	2 (2.8)	2 (7.1)	0 (0)	0 (0)	0 (0)
HPV 17	8 (11.1)	3 (10.7)	2 (11.1)	1 (16.7)	2 (10.0)
HPV 22	7 (9.7)	4 (14.3)	0 (0)	0 (0)	3 (15.0)
HPV 23	5 (6.9)	4 (14.3)	0 (0)	0 (0)	1 (5.0)
HPV 37	1 (1.4)	0 (0)	0 (0)	0 (0)	1 (5.0)
HPV 38	12 (16.7)	6 (21.4)	2 (11.1)	1 (16.7)	3 (15.0)
HPV 80	6 (8.3)	3 (10.7)	1 (5.6)	1 (16.7)	1 (5)

		Pathological Diagnosis N (%)			
	Total n=72	Condyloma n=28	Probable condyloma[a] n=18	PeIN n=6	Other[b] n=20
HPV species/type	N (%)	N (%)	N (%)	N (%)	N (%)
β3					
Any β3	3 (4.2)	1 (3.6)	0 (0)	0 (0)	2 (10.0)
HPV 49	1 (1.4)	0 (0)	0 (0)	0 (0)	1 (5)
HPV 75	3 (4.2)	1 (3.6)	0 (0)	0 (0)	2 (10.0)
HPV 76	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
β4					
HPV 92	1 (1.4)	1 (3.6)	0 (0)	0 (0)	0 (0)
β5					
HPV 96	5 (6.9)	2 (7.1)	0 (0)	0 (0)	3 (15.0)
Multiple β-HPV infections					
β-HPV negative	28 (38.9)	6 (21.4)	12 (66.7)	4 (66.7)	6 (30.0)
1 type	17 (23.6)	7 (25.0)	3 (16.7)	0 (0)	7 (35.0)
2 types	13 (18.1)	8 (28.6)	1 (5.6)	1 (16.7)	3 (15.0)
≥3 types	14 (19.4)	7 (25.0)	2 (11.1)	1 (16.7)	4 (20.0)

PeIN: Penile intraepithelial neoplasia (I, II, or III).

[a] Includes lesions suggestive but not diagnostic of HPV or condyloma.

[b] Includes various HPV-unrelated skin conditions, such as seborrheic keratosis and skin tags.

Table 3

Beta (β)-HPV Type Distribution Among Newly Detected, Pathologically Confirmed Condyloma and PeIN (n=34), by Mucosal Alpha (α)-HPV Status

	Condyloma n=28			PeIN n=6		
	α HPV 6/11- n=6[a]	α-HPV 6/11+ n=22b		α-HPV 16/18- n=3[a]	α-HPV 16/18+ n=3[b]	
HPV species/type	**N (%)**	**N (%)**	**P[c]**	**N (%)**	**N (%)**	**P[c]**
Any β-HPV type	5 (83.3)	17 (77.3)	1.000	1 (33.3)	1 (33.3)	1.000
β1						
Any β1	2 (33.3)	16 (72.7)	0.153	1 (33.3)	1 (33.3)	1.000
HPV 5	1 (16.7)	5 (22.7)	1.000	0 (0)	0 (0)	NA
HPV 8	0 (0)	5 (22.7)	0.314	0 (0)	0 (0)	NA
HPV 12	0 (0)	3 (13.6)	0.574	0 (0)	0 (0)	NA
HPV 14	1 (16.7)	4 (18.2)	1.000	0 (0)	0 (0)	NA
HPV 21	1 (16.7)	1 (4.5)	0.388	1 (33.3)	1 (33.3)	1.000
HPV 24	0 (0)	2 (9.1)	1.000	0 (0)	0 (0)	NA
HPV 36	0 (0)	3 (13.6)	0.579	0 (0)	0 (0)	NA
HPV 47	0 (0)	3 (13.6)	0.578	0 (0)	0 (0)	NA
β2						
Any β2	2 (33.3)	11 (50)	0.653	1 (33.3)	1 (33.3)	1.000
HPV 9	0 (0)	2 (9.1)	1.000	0 (0)	1 (33.3)	1.000
HPV 15	0 (0)	2 (9.1)	1.000	0 (0)	0 (0)	NA
HPV 17	0 (0)	3 (13.6)	0.578	1 (33.3)	0 (0)	1.000
HPV 22	0 (0)	4 (18.2)	0.550	0 (0)	0 (0)	NA
HPV 23	0 (0)	4 (18.2)	0.553	0 (0)	0 (0)	NA
HPV 38	2 (33.3)	4 (18.2)	0.576	0 (0)	1 (33.3)	1.000
HPV 80	1 (16.7)	2 (9.1)	1.000	0 (0)	1 (33.3)	1.000
β3						
Any β3	0 (0)	1 (4.5)	1.000	0 (0)	0 (0)	NA
HPV 75	0 (0)	1 (4.5)	1.000	0 (0)	0 (0)	NA
β4						
HPV 92	0 (0)	1 (4.5)	1.000	0 (0)	0 (0)	NA

	Condyloma n=28			PeIN n=6		
	α HPV 6/11- n=6[a]	α-HPV 6/11+ n=22b		α-HPV 16/18- n=3[a]	α-HPV 16/18+ n=3[b]	
HPV species/type	**N (%)**	**N (%)**	**P[c]**	**N (%)**	**N (%)**	**P[c]**
β5						
HPV 96	1 (16.7)	1 (4.5)	0.387	0 (0)	0 (0)	NA
Multiple β-HPV infections						
β-HPV negative	1 (16.7)	5 (22.7)	NA	2 (66.7)	2 (66.7)	NA
1 type	3 (50.0)	4 (18.2)	NA	0 (0)	0 (0)	NA
2 types	2 (33.3)	6 (27.3)	NA	1 (33.3)	0 (0)	NA
≥3 types	0 (0)	7 (31.8)	NA	0 (0)	1 (33.3)	NA

PeIN: Penile intraepithelial neoplasia (I, II, or III); NA: Not available.

[a] Negative for both α-HPV types.

[b] Positive for one or both α-HPV types.

[c] Exact Pearson chi-square *P* value using Monte Carlo estimation.

Table 4

Proportion of beta (β)-HPV DNA-positive external genital lesions (EGL) (n=72) with HPV of the same genotype detected, and not detected, on normal genital skin 6–12 months prior to lesion detection

	β-HPV detected on normal genital skin 6–12 months prior to lesion[a]	β-HPV not detected on normal genital skin 6–12 months prior to lesion[b]
HPV species/type	**N (%)**	**N (%)**
β1		
HPV 5	9 (81.8)	2 (18.2)
HPV 8	4 (66.7)	2 (33.3)
HPV 12	6 (66.7)	3 (33.3)
HPV 14	4 (57.1)	3 (42.9)
HPV 20	2 (66.7)	1 (33.3)
HPV 21	3 (50.0)	3 (50.0)
HPV 24	4 (80.0)	1 (20.0)
HPV 36	5 (100)	0 (0)
HPV 47	2 (50.0)	2 (50.0)
HPV 93	0 (0)	1 (100)
β2		
HPV 9	3 (50.0)	3 (50.0)
HPV 15	2 (100)	0 (0)
HPV 17	4 (50.0)	4 (50.0)
HPV 22	5 (71.4)	2 (28.6)
HPV 23	4 (80.0)	1 (20.0)
HPV 37	1 (100)	0 (0)
HPV 38	11 (91.7)	1 (8.3)
HPV 80	4 (66.7)	2 (33.3)
β3		
HPV 49	0 (0)	1 (100)
HPV 75	3 (100)	0 (0)
β4		
HPV 92	1 (100)	0 (0)
β5		
HPV 96	4 (80.0)	1 (20.0)

[a] Proportion of β-HPV DNA-positive lesions that were β-HPV DNA-positive for the same genotype on normal genital skin 6–12 months prior to lesion detection.

[b] Proportion of β-HPV DNA-positive lesions that were β-HPV DNA-negative for the same genotype on normal genital skin 6–12 months prior to lesion detection.