

Human papillomavirus prevalence and behavioral risk factors among HIV-infected and HIV-uninfected men who have sex with men in Taiwan

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Abstract

Human papillomavirus (HPV) infection is associated with cancer and can be prevented through vaccination. Few studies from Taiwan have reported on HPV infection among human immunodeficiency virus (HIV)-infected subjects. The aim of this study was to examine the prevalence of HPV infection among men who have sex with men (MSM) with and without HIV infection in Taiwan, and explore the behavioral risk factors thereof.

We conducted a cross-sectional study in Taiwan during 2013 to 2016 to collect data on MSM aged 20 years or older. We used a questionnaire in a face-to-face interview, and subsequently collected oral, anal, and genital specimens from HIV-infected and HIV-uninfected subjects. Multivariate analysis was performed to predict factors associated with high-risk HPV (HR-HPV) positivity.

Overall, 279 subjects, including 166 (59.5%) HIV-uninfected and 113 (40.5%) HIV-infected men were enrolled. Compared to HPV-negative subjects, HPV-positive subjects had significantly higher rates of receptive anal sex (91.3% vs 75.6%), substance use (22.6% vs 11%), history of sexually transmitted infections (75.7% vs 38.4%), anogenital or oral warts (39.1% vs 6.72%), syphilis (32.2% vs 11.6%), and HIV infection (69.6% vs 20.1%). We detected 489 HPV deoxyribonucleic acid (DNA) types (through 379 viable specimens), of which 43.6%, 5.7%, 56.4%, and 10.4% were HR-HPV type, HPV type 16, low-risk HPV types, and HPV type 6, respectively. In multivariate analysis, HIV-infected subjects had a significantly higher prevalence of HR-HPV infection (adjusted odds ratio, 5.80; 95% confidence interval, 2.57–13.11), compared to HIV-uninfected subjects.

These results suggest that the prevalence of HPV infection was high among HIV-infected MSM. Additionally, anal HPV infection was observed to be common among both HIV-infected and HIV-uninfected MSM in Taiwan. The prevalence of oral and genital HPV infection, HR-HPV DNA types, and multiple HPV types was higher in HIV-infected subjects than in HIV-uninfected subjects. As only 35% of subjects practiced safe sex, we recommend routine HPV vaccination with 4-valent HPV or 9-valent HPV vaccines for both MSM, and HIV-infected subjects.

Abbreviations: ACIP = Advisory Committee on Immunization Practices, AOR = adjusted odds ratio, ART = antiretroviral therapy, 2vHPV = bivalent HPV vaccine, CI = confidence interval, CSMUH = Chung Shan Medical University Hospital, HIV = human immunodeficiency virus, HPV = human papillomavirus, HPV-16 = HPV type 16, HR-HPV = high-risk HPV, IQR = interquartile range, MSM = men who have sex with men, OR = odds ratio, SCC = squamous cell cancer, STI = sexually transmitted infection, 4vHPV = 4-valent HPV vaccine, 9vHPV = 9-valent HPV vaccine.

Keywords: human immunodeficiency virus, human papillomavirus, men who have sex with men, sexually transmitted infection, vaccination

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1. Introduction

Sexually transmitted infections (STIs) are a major public health issue. They can facilitate the transmission of both human immunodeficiency virus (HIV), and human papillomavirus (HPV). HPV infection is well established as the primary cause of cervical cancer and is also associated with HPV-related squamous cell cancers (SCCs), especially among men who have sex with men (MSM).^[1–3] More than 200 HPV types have been identified, and >30 are sexually transmitted; of these, 15 are considered oncogenic or high-risk HPV (HR-HPV).^[4,5] In 2008, an estimated 610,000 of 12.7 million (4.8%) new cancer cases worldwide were attributable to HPV.^[4] The difference in the prevalence of HPV-associated cancers is affected by income variation, sex, certain sexual behaviors, and immune attenuation status.^[4,6–8] The prevalence of HPV infection varies widely depending on the different ethnic groups, geographic areas, and types of samples collected among HIV-infected and HIV-uninfected MSM. Previous studies in Western countries have shown that the rate of anal HPV infection in HIV-infected men is in 97.9% in the United States, 86.1% in Mexico, and 96.3% in Italy.^[9–11] These studies have also reported the prevalence of anal HPV infection among HIV-infected MSM in Asia: 76.9% in Taiwan, 85% in Thailand, 75.9% in Japan, and 82.1% to 82.69% in China.^[12–16] The prevalence of anal HPV is higher than that of external and oral sites.^[17–19] For oral HPV infection, a meta-regression analysis showed a 17.1% pooled prevalence in HIV-uninfected MSM, and 28.9% in HIV-infected MSM.^[20] Importantly, anal HPV infection can cause more serious diseases among HIV-infected men than in HIV-negative ones.^[9,21–23]

The HPV virus is transmitted through direct skin-to-skin contact even when the infection is asymptomatic. Vertical transmission rarely occurs from mother to child.^[24] Most cases of HPV infection are transmitted through unprotected sexual contact. Oral-anogenital exposure seems to be partially responsible for the acquisition of oral HPV infections.^[24–26] Consistent condom use can reduce the risk of transmission, but the usage of condoms appears to be inconsistent.^[24,25,27] Some studies suggest a potentially lower risk of sexual transmission through circumcised men, but this is controversial.^[27,28]

The best approach to preventing HPV infection is through HPV vaccination.^[29,30] The Advisory Committee on Immunization Practices (ACIPs) recommends routine vaccination for girls and boys aged 11 to 12 years, using a 3-dose series of 4-valent (4vHPV), or 9-valent HPV vaccines (9vHPV). It is also strongly recommended for men in high risk groups, up to 26 years of age; including HIV-infected individuals, and MSM having unprotected sex with multiple partners.^[31]

More data are therefore needed on the prevalence of HPV infection in Taiwanese men.^[12,13,23,32] In a study comprising 230 HIV-infected men by in northern Taiwan, 83% had anal HPV infection.^[23] A similar previous study in southern Taiwan showed that the rate of anal HPV infection was 76.9% of 130 HIV-infected MSM.^[12] An exclusive study conducted in southern Taiwan showed that 45.3% of 205 HIV-infected MSM had genital HPV infections, and significant differences were reported in HR-HPV types between HIV-infected (31.2%) and HIV-uninfected (13.0%) subjects.^[32] There are limited number of studies on the prevalence of oral HPV among MSM infected with HIV in Asia. However, no data are available on the prevalence of oral HPV infection among HIV-infected MSM in Taiwan.

We determined the prevalence of HPV infection from oral, external-genital, and anal samples among HIV-infected

and HIV-uninfected MSM in Taiwan, and examined the behavioral risk factors thereof.

2. Methods

2.1. Subject population

We conducted this cross-sectional study between January 1, 2013, and December 31, 2016, at the Chung Shan Medical University Hospital (CSMUH), a 1162-bed medical center in Taichung City, Taiwan. Subjects were enrolled through various means as follows: HIV Voluntary Counseling and Testing Clinics at the CSMUH, outreach to MSM-frequented venues (including MSM bathhouses, gay bars, MSM gymnasiums, and MSM clubs), internet advertisements, and nongovernmental organization, or peer referrals. Eligibility criteria included male sex, age ≥ 20 years, self-reported history of having sex with men prior to the arrival of participants, willingness to provide blood samples for HIV testing, willingness to undergo oral, external genital, or anal swab sampling to test for HPV infection and HPV genotypes, and able and willing to provide written informed consent. Some were confirmed to be HIV infected while others were confirmed as being HIV uninfected. HIV infection was confirmed in those who tested positive for both enzyme-linked immunosorbent assay, and HIV western blot testing.

2.2. Data collection

The study protocol was approved by the Institutional Review Board of CSMUH (CSMUH no: CS11079). Each subject provided written informed consent for HIV and HPV testing, and completed a standardized questionnaire. Data were collected through face-to-face interviews to understand the association between HPV infection and the subjects' behaviors and other diseases they may have contracted. The information gathered included demographic data, sexual behavior, sexual partners, drug use, circumcision status, and history of STI, especially syphilis and anogenital warts, and previous HIV test results.

2.3. CD4-T-cell counts and HIV viral load

For HIV-infected subjects, we collected the data of plasma HIV viral load, CD4-T-cell count at enrollment and no information related to current antiretroviral therapy (ART) exists. CD4-T cell counts were determined with an Epics XL-MCL flow cytometer (Beckman Coulter, Brea, CA).^[23,32] Plasma HIV-1 viral loads were processed using quantitative polymerase chain reaction (PCR) (Cobas Ampliprep/Cobas TaqMan HIV-1 test; Roche Molecular Systems, Basel, Switzerland) with a detection limit of 20 copies/mL. Details on the correct procedures for these tests have been described in previous studies.^[23,32]

2.4. Human papillomavirus DNA-type detection

Samples for HPV deoxyribonucleic acid (DNA) type detection were collected using oral lavage, anal canal swab (anal and oral specimens were clinician-collected), and external genital swab (self-collected). All samples were processed at the central laboratory using PCR amplification, as described in detail in other studies.^[23,33] The Roche Linear Array HPV genotyping test (Roche Molecular Systems, Inc, Branchburg, NJ) was performed on all specimens.^[23,33] This assay is able to genotype 37 HPV types, including 15 oncogenic or HR-HPV types (16, 18, 31, 33,

35,39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), 3 probable HR types (26, 53, and 66), and 19 low-risk HPV types (6, 11, 40, 42, 54, 55, 61, 62, 64, 67, 69,70, 71,72, 81, 83, 84, IS39, and CP6108).^[24,33] Some subjects, who were unwilling, were unable to supply all 3 samples; a few samples that became contaminated were subsequently discarded.

2.5. Statistical analyses

Continuous variables were reported as median and interquartile range (IQR), while categorical data were reported as number (n) and percentage (%). We performed descriptive analysis to compare differences in demographic characteristics and sexual behaviors between HPV-positive and HPV-negative subjects. Independent 2-sample *t* tests were used for continuous variables, and Chi-squared/Fisher's exact tests were used for categorical variables. Logistic regression analysis was performed to calculate the odds ratio (OR) of significant factors associated with HR-HPV infection. Multivariate logistic regression models were then applied to significant factors found in univariate analysis. All statistical tests were 2-sided and evaluated at a .05 level of significance. Statistical analyses were performed with SPSS 21.0 Statistical Software Package (SPSS, Inc, Chicago, IL).

3. Results

3.1. Participant characteristics

We enrolled 279 eligible consenting subjects, both HIV infected and HIV uninfected, between January 2013 and December 2016. The demographic characteristics are displayed in Table 1. The median age was 26.0 years (IQR 23.0–31.0 years), with 198 (71%) subjects <30 years. Our study population included 166 (59.5%) HIV-uninfected and 113 (40.5%) HIV-infected subjects. Most subjects were unmarried (96.8%), employed (73.5%), and had university graduate or post-graduate education (83.2%).

3.2. Sexual behavior

Most subjects were homosexual or bisexual men (82.4%; $P=.003$). Compared to HPV-negative subjects, HPV-positive subjects had significantly higher rates of receptive anal sex (91.3% vs 75.6%; $P=.001$), substance use (22.6% vs 11%; $P=.009$), and history of STI (75.7% vs 38.4%; $P\leq .001$) in the 6 months prior to enrollment. Furthermore, HPV-positive subjects had higher rates of anogenital or oral warts (39.1% vs 6.72%; $P\leq .001$) and syphilis (32.2% vs 11.6%; $P\leq .001$). A higher percentage of HPV-positive subjects had HIV infection (69.6% vs 20.1%; $P<.001$) (Table 1).

3.3. Human papillomavirus prevalence

Next, we evaluated the prevalence of vaccine-preventable HPV DNA in 3 specimen types (Table 2). We detected 489 HPV DNA types (through 379 viable specimens from 279 subjects), in which 11.9% (58) were in oral swabs, 21.3% (104) in external genital swabs, and 66.9% (327) in anal swabs. Of those, 5.7% ($n=28$), 2.7% ($n=13$), 6.1% ($n=30$), 10.4% ($n=51$), and 10.4% ($n=39$) were HPV type 16 (HPV-16), HPV-18, HPV-33, HPV-6, and HPV-11, respectively. The prevalence of HPV DNA types of all specimens among the 279 HIV-infected and HIV-uninfected subjects is shown in Figure 1. The prevalence of the vaccine-preventable HPV types by the bivalent vaccine (2vHPV; HPV16/18), 4vHPV (HPV6/11/16/18), and 9vHPV (HPV6/11/16/18/31/

33/45/52/58) vaccine types were 8.4%, 26.8%, and 43.1%, respectively. Comparison of the 3 different sites showed oral specimen HPV prevalence as 3.4% (2vHPV), 13.8% (4vHPV), and 22.4% (9vHPV). HPV prevalence in external genital specimens was 9.6% (2vHPV), 31.7% (4vHPV), and 45.2% (9vHPV). HPV prevalence in anal specimens was 8.9% (2vHPV), 27.5% (4vHPV), and 46.2% (9vHPV).

Table 3 shows the prevalence of HPV types detected in different specimens between HIV-infected and HIV-uninfected subjects. Among the 279 subjects tested to determine HPV DNA types, 115 (41.2%) tested positive for HPV, of which 70.8% (80/113) were also HIV-infected. HPV DNA types were detected in 21.1% (35/166) of samples from HIV-uninfected subjects, while multiple HPV DNA types were detected in 57.5% of samples from HIV-infected subjects. We compared high-risk HPV (HR-HPV) types in HIV-uninfected to HIV-infected subjects. HR-HPV types were detected in 9.0% of HIV-uninfected and 49.6% of HIV-infected subjects. In oral samples, 3.8% HR-HPV types were detected for HIV-uninfected, vs 18.5% for HIV-infected ($P=.041$) subjects. In external genital samples, the rates were 5.8% vs 18.3%, respectively ($P<.0001$). In anal samples, the rates were 33.3% vs 64.7% ($P=.082$).

3.4. Risk factors for high-risk types of human papillomavirus

We analyzed the age, sexual orientation, and behavioral characteristics of subjects to predict the potential for HR-HPV types in HPV infection. The results for the univariate and multivariate analyses are provided in Table 4.

The univariate analysis identified independent correlations with HR-HPV types of infection, including: MSM behavior (OR, 2.82; 95% confidence interval [CI], 1.15–6.95; $P<.05$), receptive anal sex (OR, 2.90; 95% CI, 1.18–7.15; $P<.05$), drug abuse in the previous 6 months (OR, 3.38; 95% CI, 1.73–6.60; $P<.05$), STIs in the past 6 months (OR, 5.63; 95% CI, 2.91–10.89; $P<.05$), anogenital or oral warts (OR, 5.12; 95% CI, 2.74–9.57; $P<.05$), and HIV-infected (OR, 9.89; 95% CI, 5.18–18.87; $P<.05$).

The multivariate analysis included age, sexual orientation, and sexual behaviors among all HPV-infected subjects in Model 1. Subjects with warts (OR, 2.29; 95% CI, 1.06–4.95; $P<.05$) and HIV-infected subjects (OR, 2.64; 95% CI, 1.11–6.26; $P<.05$) were significantly associated with HR-HPV types. In Model 2, the analysis identified significant factors associated with HR-HPV types in univariate analysis. Subjects with warts (OR, 2.25; 95% CI, 1.04–4.84; $P<.05$), and HIV-infected subjects (OR, 6.10; 95% CI, 2.54–14.66; $P<.05$) remained significantly associated with HR-HPV types. In Model 3, all *insignificant* variables in the univariate analysis, Model 1, and Model 2 were excluded. After excluding *insignificant* variables in other analyses, HIV-infection (OR, 6.10; 95% CI, 2.54–14.66; $P<.05$) remained significantly associated with HR-HPV types in Model 3.

4. Discussion

Our study demonstrated a high prevalence of HPV infection among HIV-infected MSM. HPV prevalence was observed in 70.8% of HIV-infected, and 21.1% of HIV-uninfected subjects. The prevalence of anal HPV infection was 73.3% in HIV-uninfected and 85.3% in HIV-infected subjects. Of note, a higher rate of HR-HPV DNA types was detected in anal specimens than other specimens. There was no difference in rates between HIV-infected- and -uninfected subjects. Furthermore, our findings

Table 1**Demographic characteristics of the study subjects.**

Characteristic	Overall (n = 279; 100%) n (%)	HPV-negative (n = 164; 58.8%) n (%)	HPV-positive (n = 115; 41.2%) n (%)	P-value*
Age, median (IQR), y	26.0 (23.0–31.0)	26.0 (24.0–31.0)	26.0 (23.0–31.0)	.866
Age, y				
<30	198 (71.0)	117 (71.3)	81 (70.4)	.870
≥31	81 (29.0)	47 (28.7)	34 (29.6)	
Marital status				.741
Never married	270 (96.8)	158 (96.3)	112 (97.4)	
Married†	9 (3.2)	6 (3.7)	3 (2.6)	
Education				.001
High-school or less	47 (16.8)	17 (10.4)	30 (21.6)	
University or more	232 (83.2)	147 (89.6)	85 (73.9)	
Employment status				.335
Unemployed/disabled	74 (26.5)	40 (24.4)	34 (29.6)	
Employed	205 (73.5)	124 (75.6)	81 (70.4)	
Sexual orientation				.003
Heterosexual males	49 (17.6)	38 (23.2)	11 (9.6)	
Homosexual/bisexual males	230 (82.4)	126 (76.8)	104 (90.4)	
<i>Sex behavior</i>				
Receptive anal sex				.001
No	50 (17.9)	40 (24.4)	10 (8.7)	
Yes	229 (82.1)	124 (75.6)	105 (91.3)	
Receptive oral sex				.955
No	5 (1.8)	3 (1.8)	2 (1.7)	
Yes	274 (98.2)	161 (98.2)	113 (98.3)	
Drug use in past 6 mo				.009
No	235 (84.2)	146 (89.0)	89 (77.4)	
Yes	44 (15.8)	18 (11.0)	26 (22.6)	
Circumcised				.901
No	229 (82.1)	135 (82.3)	94 (81.7)	
Yes	50 (17.9)	29 (17.7)	21 (18.3)	
STIs in past 6 mo				.000
No	129 (46.2)	101 (61.6)	28 (24.3)	
Yes	150 (53.8)	63 (38.4)	87 (75.7)	
Currently have anogenital or oral warts				.000
No	223 (79.9)	153 (93.3)	70 (60.9)	
Yes	56 (20.1)	11 (6.7)	45 (39.1)	
One-night stand in past 6 mo				.236
No	174 (62.4)	107 (65.2)	67 (58.3)	
Yes	105 (37.6)	57 (34.8)	48 (41.7)	
Number of sex partners in lifetime				.110
<10	226 (81.0)	138 (84.1)	88 (76.5)	
≥10	53 (19.0)	26 (15.9)	27 (23.5)	
Used condom during last intercourse				.518
No	91 (32.6)	51 (31.1)	40 (34.8)	
Yes	188 (67.4)	113 (68.9)	75 (65.2)	
Used condom every time with sex partners in the past 3 mo				.441
No	182 (65.2)	110 (67.1)	72 (62.6)	
Yes	97 (34.8)	54 (32.9)	43 (37.4)	
<i>Current status of STIs</i>				
Diagnosed with syphilis				.000
No	223 (79.9)	145 (88.4)	78 (67.8)	
Yes	56 (20.1)	19 (11.6)	37 (32.2)	
Diagnosed as HIV-positive				.000
No	166 (59.5)	131 (79.9)	35 (30.4)	
Yes	113 (40.5)	33 (20.1)	80 (69.6)	
CD4 T-cell count (IQR, n = 113)	394.5 (301.3–581.3)	397.0 (324.3–583.0)	394.5 (299.8–571.5)	.972
HIV viral load (log ₁₀ , IQR, n = 113)	3.5 (1.3–4.8)	3.9 (1.4–4.7)	3.3 (1.3–4.8)	.661

CD = Cluster of Differentiation; HIV = human immunodeficiency virus; HPV = human papillomavirus; IQR = interquartile range; STI = sexually transmitted infection.

* $P < .05$.

† Marital status includes "married," "divorced," and "separated."

showed a higher anal detection rate of HPV types (compared with oral or genital) among HIV-infected subjects. The high prevalence and incidence rates of anal HPV infection among MSM, regardless of HIV infection, are well established in

previous studies. A large study in China showed the anal HPV prevalence rate in 500 HIV-uninfected MSM as 51.8%, 45.6% of whom had HR-HPV infection.^[34] Reported prevalence rates among HIV-infected and HIV-uninfected subjects are as follows:

Table 2
Prevalence of vaccine-preventable HPV by specimen type from 279 subjects.

HPV distribution	Total specimens (n=379)		Oral (n=80)		Genital (n=216)		Anal (n=83)	
	n	%	n	%	n	%	n	%
Number of HPV DNA	489		58		104		327	
Number of 2vHPV	41	8.4	2	3.4	10	9.6	29	8.9
16	28	5.7	1	1.7	6	5.8	21	6.4
18	13	2.7	1	1.7	4	3.8	8	2.5
Number of 4vHPV	131	26.8	8	13.8	33	31.7	90	27.5
6	51	10.4	4	6.9	16	15.4	31	9.5
11	39	8.0	2	3.5	7	6.7	30	9.2
16	28	5.7	1	1.7	6	5.8	21	6.4
18	13	2.7	1	1.7	4	3.8	8	2.4
Number of 9vHPV	211	43.1	13	22.4	47	45.2	151	46.2
6	51	10.4	4	6.9	16	15.4	31	9.5
11	39	8.0	2	3.5	7	6.7	30	9.2
16	28	5.7	1	1.7	6	5.8	21	6.4
18	13	2.7	1	1.7	4	3.8	8	2.4
31	7	1.4	0	0	2	1.9	5	1.5
33	30	6.1	2	3.5	5	4.8	23	7.0
45	5	1.0	1	1.7	1	1.0	3	0.9
52	14	2.9	0	0	3	2.9	11	3.4
58	24	4.9	2	3.5	3	2.9	19	5.9

2vHPV = bivalent vaccine (16/18), 4vHPV = quadrivalent vaccine HPV type (6/11/16/18), 9vHPV = 9-valent vaccine HPV type (6/11/16/18/31/33/45/52/58), HPV = human papillomavirus.

91.6% vs 65.9% in the United States (in 2013), 85% vs 58.5% in Thailand (in 2013), 82.1% vs 57.5% in China (in 2013), 82.69% vs 62.81% in China (in 2016), and 96.3% vs 70.6% in Italy (in 2018).^[11,14–16,35] Hence, our findings were similar to those of previous studies.^[11,14–16,35] Regarding the high prevalence of anal HPV infection, the risk of anal HPV infection may result from increased sexual exposure, or anal mucosa trauma due to not using condoms; the main pathogenesis of anal HPV infection, however, is not well known.^[13,35] HIV infection decreases the ability of the immune system to clear HPV, and the persistence of anal HPV infection among MSM could be related to higher anal detection.^[9,16]

Early post-ART studies have indicated that HPV-associated malignancies occur at increased rates in HIV-infected subjects.^[1,36] Due to the success of ART, the incidence of AIDS-defining cancers have dramatically declined during the last decade, and the incidence of non-AIDS-defining cancers appears to have been uninfluenced in HIV-infected subjects.^[37] The results from our multivariate model highlighted that HIV-infection among MSM was a significant factor (OR, 5.8; 95% CI, 2.57–13.11) for infection with HR-HPV DNA types. The results of our study are concordant with those of previous studies, showing that HIV-infected MSMs have a strong association with HR-HPV infection.^[16,38] HIV-infected subjects have an increased

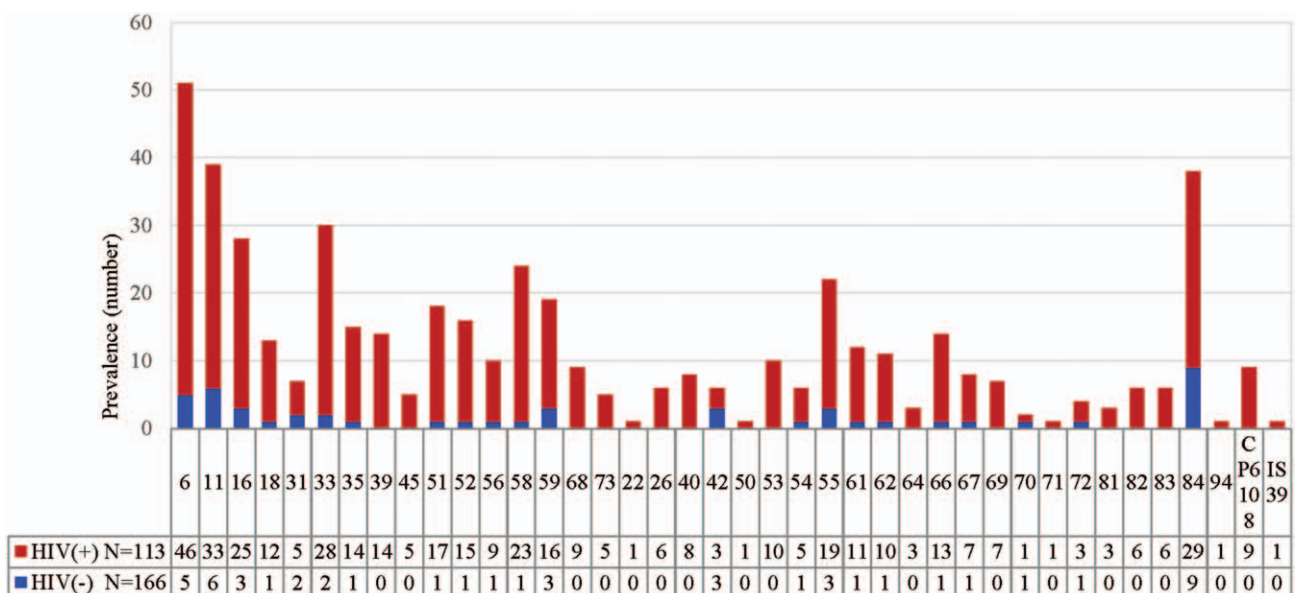


Figure 1. Differences in HPV prevalence by number of DNA types among HIV-infected and HIV-uninfected men (N=279). HIV = human immunodeficiency virus, HPV = human papillomavirus.

Table 3**Prevalence of HPV types detected in 379 different specimens collected from 279 HIV-infected and HIV-uninfected subjects.**

Site of detection	HPV type	HIV-negative (n=166; 59.5%)		HIV-positive (n=113; 40.5%)		P-value*
		n (%)	n (%)	n (%)	n (%)	
All sites	None	131 (78.9)		33 (29.2)		.000
	Any HPV	35 (21.1)		80 (70.8)		
	Low-risk HPV	20 (12.0)		24 (21.2)		.039
	High-risk HPV	15 (9.0)		56 (49.6)		.000
	Multiple†	14 (8.4)		65 (57.5)		.000
Oral samples	No	15 (57.7)		15 (57.7)		.041
	Low-risk HPV	10 (38.5)		9 (16.7)		
	High-risk HPV	1 (3.8)		10 (18.5)		
External genital samples	No	138 (88.4)		33 (55.0)		.000
	Low-risk HPV	9 (5.8)		16 (26.7)		
	High-risk HPV	9 (5.8)		11 (18.3)		
Anal samples	No	4 (26.7)		10 (14.7)		.082
	Low-risk HPV	6 (40.0)		14 (20.6)		
	High-risk HPV	5 (33.3)		44 (64.7)		

HPV = human papillomavirus, HIV = human immunodeficiency virus.

* $P < .05$.

† Multiple = 2 or more HPV types.

risk of developing HPV-associated cancers.^[1] However, as recently reported, immunosuppression may not be the only independent determinant of the pathogenesis of HPV-associated cancers in HIV-infected subjects; the direct interaction between HIV and HPV-16 or HR-HPV DNA types may contribute to this pathogenesis.^[39,40]

HPV-16 and HPV-18 were the types most commonly associated with the cause of SCC of the penis, anus, rectum, and oropharynx in men.^[4,8,41] Our findings revealed that HIV-infected subjects have a higher prevalence of HR-HPV DNA types, with HPV-16 and HPV-33 being the type most frequently detected, particularly in anal samples. HR-HPV types were detected in 9.0% of HIV-uninfected and 49.6% of HIV-infected subjects. Recent studies have shown that HPV-16 infection in HIV-infected men and its integration in anal cells could be a promising biomarker for predicting anal precancerous lesions.^[42] The screening programs for HPV infection may have the potential to reduce HPV-associated cancer in HIV-infected subjects or MSM.

Our study collected samples from 3 sites, which is not very common in such studies.^[3,11,17,19,32,43] Limited studies have focused on HPV infection in external genital sites in HIV-infected subjects in Asia, including Taiwan. In our study, external genital swab HPV prevalence in HIV-uninfected, compared to HIV-infected subjects was 11.6% vs 45.0%. A genital HPV study in Taiwan reported that HPV infection was more common in HIV-infected MSM than in HIV-uninfected subjects (45.3% vs 18.0%), and a significant difference was reported in HR-HPV types between HIV-infected (31.2%), and HIV-uninfected (13.0%) subjects.^[32] A previous study of HIV-infected men showed that a higher prevalence of HR-HPV types were present in the penises of MSM, than in heterosexual subjects (38% vs 32%).^[17] The results of our study were consistent with those of previous studies.^[11,17,32] Our results showed a lower prevalence of genital HPV infection with discordant findings among circumcised subjects (17.9%), and consistent condom use (34.8%). HIV infection could possibly be considered a risk factor for clearance and persistence of HPV infection.

Regarding HPV-related cancers, previous studies have reported the presence of HPV infection in oropharyngeal

cancer.^[44,45] The prevalence of oral HPV infection is less common than external and anal sites.^[17-19] A meta-regression analysis on oral HPV infection showed a 17.1% pooled prevalence in HIV-uninfected MSM, and 28.9% in HIV-infected subjects.^[20] The detection of HPV infection from oral specimens in HIV-uninfected and HIV-infected subjects was 42.3% vs 35.2%. Several studies have reported the prevalence of oral HPV infection among HIV-infected and HIV-uninfected MSM worldwide, 11.2% in Canada, 30% in Spain, 6.1% vs 8.3% for the HIV-infected and HIV-uninfected subjects in Italy, 2017, and 21.6% vs 29.4% for the HIV-infected and HIV-uninfected subjects in Italy, 2018.^[11,17,25,46] Our result on the prevalence of oral HPV infection was more distinct than those of previous studies.^[11,17,20,25,46] The concordance rate between oral and anal HPV infections among MSM may relate to the different modes of HPV clearance, as well as acquiring infection through different sexual practices.^[3,18] Since persistent HR-HPV types seem to be related to the development of oropharyngeal cancer among HIV-infected subjects, the detection of oral HPV DNA is important, even if the detection rate is low.

The HPV vaccination is recommended to prevent infection and subsequent development of HPV-related sequelae.^[29,30] In our study, the coverage rates for bivalent, 4vHPV, and 9vHPV vaccines were 8.4%, 26.8%, and 43.1%, respectively. A Taiwanese study in HIV-infected men reported similar bivalent, 4vHPV, and 9vHPV vaccine coverage rates of 24.8%, 46.9%, and 52.2%, respectively.^[23] Our results are similar to those of a previous study of anogenital specimens in MSM, in which the prevalence of vaccine-preventable HPV for bivalent, 4vHPV, and 9vHPV vaccines were 17.0%, 32.5.8%, and 45.4%, respectively.^[47] Our findings indicate that the 9vHPV vaccine has the potential of being more cost-effective than other vaccines in protecting men, especially the MSM, including HIV-infected subjects. An ongoing national school-based HPV vaccination program with 4vHPV for young girls aged 12 to 26 years from 2007 in Australia.^[48] This real world data have shown that a decline has occurred in the number of genital warts diagnosed in heterosexual men, also probably due to herd immunity.^[48] Scaling up HPV vaccinations could provide more effective herd immunity for the MSM community, and HIV-infected subjects.

Table 4**Logistic regression analysis to predict the potential for high risk types of HPV infection.**

Variables	% (High-risk/HPV+)	Univariate analysis		Multivariate analysis		
		Crude OR (95% CI)	Model 1* Adjusted OR (95% CI)	Model 2† Adjusted OR (95% CI)	Model 3‡ Adjusted OR (95% CI)	
Men with high-risk HPV infection	61.7 (71/115)					
Age, y						
<30	64.2 (52/81)	1.00	1.00	1.00	–	
≥31	55.9 (19/34)	0.86 (0.47–1.57)	0.81 (0.39–1.68)	0.82 (0.40–1.70)	–	
Sexual orientation						
Heterosexual males	54.5 (6/11)	1.00	1.00	1.00	1.00	
Homosexual/bisexual males	62.5 (65/104)	2.82 (1.15–6.95) [§]	0.92 (0.08–11.07)	0.78 (0.08–8.15)	0.65 (0.07–5.85)	
Sexual behavior						
Receptive anal sex						
No	60.0 (6/10)	1.00	1.00	1.00	1.00	
Yes	61.9 (65/105)	2.90 (1.18–7.15)*	1.07 (0.09–12.26)	0.89 (0.09–8.80)	1.27 (0.15–10.88)	
Receptive oral sex						
No	100 (2/2)	1.00	1.00	–	–	
Yes	61.1 (69/113)	0.51 (0.08–3.09)	0.11 (0.01–1.17)	–	–	
Drug use in past 6 mo						
No	80.8 (21/26)	1.00	1.00	1.00	1.00	
Yes	56.2 (50/89)	3.38 (1.73–6.60) [§]	2.04 (0.88–4.75)	1.99 (0.86–4.60)	1.99 (0.93–4.29)	
Circumcised						
No	60.6 (57/94)	1.00	1.00	1.00	–	
Yes	66.7 (14/21)	1.17 (0.59–2.33)	1.05 (0.45–2.49)	1.01 (0.43–2.38)	–	
STIs in past 6 mo						
No	46.4 (13/28)	1.00	1.00	1.00	1.00	
Yes	66.7 (58/87)	5.63 (2.91–10.89) [§]	1.62 (0.62–4.25)	1.47 (0.58–3.75)	1.56 (0.64–3.80)	
Currently have anogenital or oral warts						
No	58.6 (41/70)	1.00	1.00	1.00	1.00	
Yes	66.7 (30/45)	5.12 (2.74–9.57) [§]	2.29 (1.06–4.95) [§]	2.25 (1.04–4.84) [§]	1.96 (0.94–4.07)	
One-night stand in past 6 mo						
No	61.2 (41/67)	1.00	1.00	1.00	–	
Yes	62.5 (30/48)	1.30 (0.75–2.25)	1.55 (0.75–3.18)	1.49 (0.73–3.05)	–	
Number of sex partners in lifetime						
<10	62.5 (55/88)	1.00	1.00	1.00	–	
≥10	59.3 (16/27)	1.34 (0.70–2.60)	0.82 (0.33–2.08)	0.85 (0.34–2.13)	–	
Used condom during last intercourse						
No	62.5 (25/40)	1.00	1.00	1.00	–	
Yes	61.3 (46/75)	0.86 (0.49–1.51)	0.55 (0.25–1.20)	0.53 (0.25–1.14)	–	
Used condom every time with sex partners in the past 3 mo						
Never	66.7 (48/72)	1.00	1.00	1.00	–	
Every time	53.5 (23/43)	0.87 (0.49–1.54)	0.89 (0.41–1.96)	0.95 (0.44–2.07)	–	
Diagnosed with syphilis						
No	56.4 (44/78)	1.00	1.00	1.00	–	
Yes	73.0 (27/37)	3.79 (2.04–7.04)	1.40 (0.65–3.02)	1.50 (0.69–3.24)	–	
Diagnosed as HIV positive						
No	42.9 (15/35)	1.00	1.00	1.00	1.00	
Yes	70.0 (56/80)	9.89 (5.18–18.87) [§]	5.77 (2.37–14.04) [§]	6.10 (2.54–14.66) [§]	5.80 (2.57–13.11) [§]	

CI=confidence interval, HIV=human immunodeficiency virus, HPV=human papillomavirus, OR=odds ratio, STI=sexually transmitted infection.

* Model 1: included all of the variables.

† Model 2: included all significant factors associated with HR-HPV types in univariate analysis.

‡ Model 3: all variables that showed insignificant association at the univariate level or in Models 1 and 2 with high risk HPV infection were excluded from Model 3.

§ $P < .05$.

A study in the United States has reported that the prevalence of penile HPV infection increases with an increase in the number of lifetime sex partners and condom use intermittently among men.^[27] In univariate analysis, MSM, receptive anal sex, drug abuse, STIs, anogenital or oral warts, and HIV infected were all significantly associated with HR-HPV infection. However, in multivariate analysis, being HIV infected was independently associated with HR-HPV infection. Consistent condom use is warranted among

high-risk populations for preventing HPV infection according to previous studies.^[27,49] In the present study, condom use with sexual partners in the previous 3 months in HR-HPV-infected subjects was low (37.4%); and 62.5% of HR-HPV-infected subjects reported not having used condoms the last time they had sex. These findings could be the possible reasons for the relationship between sexual orientation (MSM) and other risk behaviors of infection with HR-HPV DNA types was not significant.

The study has some limitations. We did not perform anal pap smears or cytology on any subject. To prevent cervical cancer, it is essential that vaginal pap smears are performed in women. Similarly, for the MSM community, including HIV-infected subjects, anal pap smears, cytology, or HPV DNA detection should be performed to screen for HPV-related cancers.^[2,3] We did not include smoking history as a risk factor of HPV infection because of a correlation between smoking and increased risk of anal precancer among HR-HPV-infected men, which had no association with HPV infection.^[6,50] However, our study focused on sexual behaviors in high-risk groups. Given that HIV-uninfected subjects were our control group, we included CD4-T-cell count test and HIV viral load results among HIV-infected subjects. In previous studies, nadir CD4-T-cell count (<350 or much lower than 200 cells/mm³) seemed to be associated with an increased risk of HR-HPV infection in HIV-infected MSM.^[6,32]

In conclusion, the prevalence of HPV infection was high among HIV-infected MSM. Additionally, anal HPV infection was observed to be common among both HIV-infected and HIV-uninfected MSM in Taiwan. The prevalence of oral and external genital HPV infection, HR-HPV DNA types, and multiple (over 2) types was significantly higher in HIV-infected subjects. Our results do not fully clarify the importance of safe sexual behaviors and constant condom use. We recommend routine HPV vaccination with 4vHPV or 9vHPV vaccines for the MSM community, including HIV-infected subjects. To effectively prevent HPV-related diseases, further research is necessary to understand the benefits of 4vHPV and 9vHPV vaccinations for both men and women.

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