# Prevalence of Anal Human Papillomavirus Vaccine Types in the Bangkok Men Who Have Sex With Men Cohort Study

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**Background:** The quadrivalent human papillomavirus (qHPV) and 9 valent (nHPV) vaccine are licensed for males to prevent anal HPV–associated dysplasia and cancer caused by HPV types 6, 11, 16, and 18 (qHPV) and additional types 33, 35, 45, 52, and 58 (nHPV), respectively. Both conditions are common in HIV-infected and HIV-uninfected men who have sex with men (MSM). It is not well documented which anal HPV vaccine types are most prevalent in Southeast Asia.

**Methods:** A convenience sample of 400 anal swabs were obtained from 200 HIV-infected and 200 HIV-uninfected sexually active Bangkok MSM Cohort Study participants. After swab collection in PreservCyt (Cytyc Corp, Marlborough, MA), the media was stored at −80°C until processing. DNA was extracted, amplified by polymerase chain reaction, denatured, and then hybridized to probes for 37 HPV types and β-globin.

**Results:** The mean participant age was 25.6 years (range, 18–55 years); the mean CD4 T-cell count was 410 cells/mm$^3$ in the HIV-infected participants. Among all swab samples, 386 (192 HIV-positive and 194 HIV-negative) had adequate β-globin for HPV genotype testing. Anal HPV type was detected in 44.3% of participants whose samples underwent genotype testing. Both qHPV and nHPV types were more frequently detected in HIV-infected compared with HIV-uninfected (42.2% vs. 23.2% [$P < 0.01$], 50.0% vs. 24.2% [$P < 0.01$]), respectively). There were no significant relationships between social behaviors (alcohol use, drug use) or sexual behaviors (number of partners, condom usage, sexual positioning) and anal HPV prevalence.

**Conclusions:** The prevalence of anal vaccine HPV types in Thai MSM was similar to that reported in MSM from Western populations and has a similar distribution by HIV status. Targeting young MSM with vaccination could offer protection against HPV vaccine types.

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We are grateful to the participants of the Bangkok Men Who Have Sex With Men Cohort Study. In addition, we are grateful to Sarika Pattanasin for her assistance in securing data for the project; Eileen Dunne, Wipas Wimonsate, and Anupong Chitwarakorn for their critical review of the final manuscript; and Shaun Burneisen for his laboratory work on human papillomavirus detection.

Conflict of Interest: R.D.C. has received institutional research funding from Merck and Co.

Presented in abstract: International Papillomavirus Meeting; San Juan, Puerto Rico; 2012.

Funding source: US Centers for Disease Control and Prevention.

Contributions: Study conception/design: R.D.C., I.M., F.V.G., M.E.C., S.C. Study sample collection: S.C., W.C. Study data analysis and interpretation: R.D.C., A.D.A., I.M., F.V.G., M.E.C., W.C., T.H.H. Involvement in drafting and revising the manuscript: R.D.C., I.M., A.D.A., F.V.G., M.E.C., S.C., W.C., T.H.H. Gave approval of the final draft for publication: R.D.C., I.M., A.D.A., F.V.G., L.J., A.S., M.E.C., T.H.H., S.C., W.C. Overall responsibility for accuracy and integrity of the research: R.D.C., I.M., F.V.G., M.E.C., T.H.H.

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Received for publication March 26, 2015, and accepted September 23, 2015.
DOI: 10.1097/OLQ.0000000000000372



The worldwide incidence of human papillomavirus (HPV)–associated anal cancer is increasing in both men and women, with current annual rates in the United States approximating 2/100,000.[1] In men who have sex with men (MSM), the incidence is similar to that of cervical cancer before the introduction of cervical cytology screening and is approximately 2 to 3 times this rate in HIV-infected MSM.[2,3]

Approximately 40 HPV types infect the anogenital area, and these can be broadly differentiated into high-risk (HR) and low-risk types based on their historical association with cervical cancer. More than 80% of all anal cancers are related to persistent infection with HR-HPV infection, with HPV type 16 being the most commonly isolated.[4]

Anal HPV–associated disease due to HPV types 6 and 11 (low-risk) and types 16 and 18 (HR) may be prevented in men with the use of the quadrivalent HPV vaccine (qHPV) Gardasil (Merck and Co, Whitehouse Station, NJ).[5,6] This vaccine is indicated for males and females aged 9 to 26 years, with optimal efficacy seen in individuals without evidence of current or past HPV infection.[6] A vaccine with increased valency that additionally incorporates HR-HPV types 31, 33, 45, 52, and 58 (nHPV) Gardasil 9 (Merck and Co) has recently been approved by the US Food and Drug Administration for boys aged 9 to 15 years.

In Western populations, the prevalence of anal HPV infection in MSM varies from study to study. Several studies report anal HPV prevalence rates of 45% to 70% in HIV-uninfected and 65% to 96% in HIV-infected MSM,[7–9] and in a recent meta-analysis of HIV-infected MSM, HPV16 was the most frequently detected type at 35.4% (95% confidence interval, 32.9–37.9).[10] In general, HIV-infected MSM also have an increased prevalence of all HPV infections, HR-HPV, and multiple HPVs, compared with HIV-uninfected MSM.[10,11]

Although the qHPV was approved by the Thai Food and Drug Administration in 2007, limited information is available

regarding HPV vaccine types prevalent in Southeast Asia, with few studies of anal HPV in Thai MSM specifically. One study in Bangkok found that any HPV type was present in 58.5% and 85.0%, and HR-HPV in 36.6% and 57.5% of 123 HIV-uninfected and 123 HIV-infected MSM, respectively, with HPV16 being the most common HR-HPV detected.[12]

This study aimed to increase the information available on anal HPV infection in Thai MSM, and in particular to define prevalence of HPV infection and risk factors as they relate to both qHPV and nHPV vaccines. These data, although of general interest in this understudied population, are also of local interest to help inform national immunization policy and guidelines in a population of HIV-infected and HIV-uninfected Thai MSM at risk for developing anal cancer.

## MATERIALS AND METHODS

The Bangkok MSM Cohort study was established in 2006 as part of the US Centers for Disease Control and Prevention (CDC) collaboration with the Thailand Department of Disease Control of the Ministry of Public Health.[13,14] The main study protocol was reviewed and approved by the Thailand Ministry of Public Health Ethical Review Committee and by a CDC institutional review board. Written informed consent was obtained from all participants. For the HPV substudy, approval was sought and obtained from the CDC to ship a convenience sample of frozen anal swab specimens obtained between 2006 and 2010 from 200 HIV-infected and 200 HIV-uninfected participants to the University of Pittsburgh for HPV testing. Approval was also obtained for this study from the University of Pittsburgh Institutional Review Board.

### Population

The study location was a dedicated men's sexual health clinic in a central Bangkok hospital. Eligible men were at least 18 years old, were Thai national, were resident of Bangkok or adjacent provinces, had a history of penetrative male-to-male sex in the 6 months before recruitment, and were available for follow-up visits every 4 months for 3 to 5 years. Men were recruited from entertainment venues (bars, discos, and saunas), parks, community-based organizations, the Internet, and by word of mouth. Men received pretest and posttest HIV and risk behavior counseling during every study visit. Those testing positive for HIV infection were referred for antiretroviral treatment according to Thai national guidelines. Those with active sexually transmitted infections were treated, and those without hepatitis B virus immunity were offered hepatitis B virus vaccination, free of charge. A total of 1744 men were recruited, all of whom had anal swab samples taken at the initial visit.

### Data Collection

Demographic, behavioral, and clinical data were collected by computer-assisted self-interview. Data on concomitant infections were available from the parent Bangkok MSM Cohort Study as previously described.[13,14] It should be noted that no information was collected on history of HPV vaccination, or on any clinical markers of HPV infection such as anal warts or other anal conditions; neither was anal cytology collected.

### Anal HPV Sample Collection

Specimens for HPV testing were obtained by study clinical staff once at the main study baseline visit by inserting a water-moistened polyester swab into the anal canal, rotating the swab and then withdrawing. The swab was immediately placed into a Digene Sampler tube and frozen at −80°C. For this study, a convenience sample of 400 anal swab samples were chosen from 200 HIV-infected and 200 HIV-uninfected study participants. The HPV media was thawed at room temperature for 30 minutes and vortexed for at least 5 seconds, and then an aliquot of 200 μL of fluid was removed. The aliquot was immediately refrozen at −80°C. Samples were shipped on dry ice from Bangkok to Pittsburgh, where they were again stored at −80°C before processing.

### HPV Detection

***DNA Extraction and β-Globin Quantification***. DNA was extracted from anal swabs using the QIAamp DNA Investigator Kit (Qiagen, Valencia, CA). DNA content was assessed by optical density on the NanoVue spectrophotometer (GE Healthcare Bio-Sciences Corp, Piscataway, NJ), and human β-globin content was determined by quantitative real-time polymerase chain reaction (PCR). β-Globin was quantified as a measure of sample collection efficiency, DNA extraction efficiency, and verification of the absence of PCR inhibitors in the extract.[15]

***Reverse Line Blot Assay***. Samples that tested positive for β-globin and/or HPV by the EvaGreen assay were analyzed for HPV subtype by the reverse line blot assay.[16] Probes specific for 37 different HPV subtypes (HPV types 6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 66, 68, 70, 71, 72, 73, 81, 82 (MM4), 82 (IS39), 83, 84, and CP6108) were covalently attached to negatively charged Biodyne C membranes (Pall Corp, Port Washington, NY) with the aid of a blotting apparatus with 45 channels (Miniblotter 45; Immunetics, Boston, MA). Probes for the individual subtypes, labeled at the 5′ end with an amino group and 6-carbon spacer, were covalently attached to the membrane through the use of a coupling reagent (EDC; Thermo Scientific, Pittsburgh, PA). In preparation for hybridization of denatured, biotinylated GP5+/GP6+ PCR products to the covalently attached probes, the blot was rotated in the apparatus 90° to result in a checkerboard pattern. Thus, each sample was hybridized simultaneously to 37 covalently applied probes for HPV subtypes and β-globin. Ten-microliter aliquots of the PCR reactions were denatured and hybridized to the blots. After hybridization, the blots were washed to remove nonspecifically bound products and incubated with streptavidin-horseradish peroxidase conjugate (GE Healthcare). Specifically bound PCR products were detected by enhanced chemiluminescence, and signals were detected on a Chemi-Doc XRS+ Molecular Imager (Bio-Rad, Hercules, CA).

### Serological Testing

Herpes simplex virus (HSV) type 2 antibody testing used the HerpeSelect 2 ELISA IgG (Focus Diagnostic, Cypress, CA) and results were reported as index value relative to the cutoff calibrator (index value = specimen optical density [OD] divided by mean of cutoff calibrator OD). A positive result for the presence of IgG antibodies to HSV-2 defined by an index value greater than 1.10. Herpes simplex virus type 1 antibodies were detected using the HerpeSelect 1 ELISA IgG kit (Focus Diagnostic). Results were reported as index values relative to the cutoff calibrator (where index value = specimen optical density divided by mean cutoff calibrator optical density). An index value greater than 1.10 was used to identify positive results, according to the manufacturer's instructions. To reduce the likelihood of false-positive results using this index for HSV types 1 and 2, samples with an index value greater than 1.10 but less than 3.5 were repeated in duplicate. In cases where 1 or both of 2 repeat tests remained greater than 1.10, a positive result was confirmed. If both repeated tests' index values were less than 1.10, the test was considered to be negative. Hepatitis A virus antibody testing used the Monolisa Total Anti-HAV Plus (Bio-Rad, Marnes-la-Coqueete, France) using an inhibition enzyme immunoassay. Results were reported as ratio value relative

to the calculated cutoff value (ratio value = mean of cutoff OD divided by mean of sample OD). Samples with a ratio value greater than or equal to 1.10 are considered to be positive. Hepatitis B surface antigens and antibodies were determined qualitatively using a hemagglutination assay (Serodia, FUGIREBIO Inc, Tokyo Japan), or 1 of 2 enzyme immunoassays (Murex [Abbott Diagnostics, Kyalami, South Africa] or Monolisa [Bio-Rad, Marnes-la-Coquette, France]) depending on kit availability. Hepatitis B virus core antibodies were determined using a competitive enzyme immunoassay (ETI-AB-COREK PLUS; DiaSorin, Saluggia, Italy) or 1 of 2 enzyme immunoassays (Murex [Abbott Diagnostics] or Monolisa [Bio-Rad]).

## Statistical Analyses

Data were summarized as mean and SD for continuous variables and percentages for categorical variables. Participant demographic characteristics, proportions with serologic evidence of selected infections (hepatitis A, hepatitis B, and HSV types 1 and 2), and HPV prevalence among HIV-infected participants versus HIV-uninfected participants were compared using $t$ tests for continuous variables and $\chi^2$ tests for categorical variables. Because of the observed differences between HIV-infected and HIV-uninfected participants and the ensuing likelihood that HIV status will influence relationships between various risk factors, behaviors, and HPV status, all further analyses were stratified by HIV status. For each HPV type investigated, $\chi^2$ tests were used to compare the proportion of participants with and those without each of the concomitant infections (based on serostatus). Relationships between categorical variables on sexual partners/behavior and HPV types were also assessed using $\chi^2$ tests. $P$ values less than 0.05 were considered statistically significant; no adjustments were made for multiple comparisons. All statistical analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC).

## RESULTS

Study participants were generally young (mean age, 25.6 years; range, 18–55 years), and most had at least a high school education (88.5%). Drug use in the last 4 months was significantly more common in HIV-infected participants (49.5% vs. 35.6%, $P < 0.01$) than in HIV-uninfected participants. Although 20.2% of participants reported drinking alcohol once or more per week, this was similar regardless of HIV status. Among HIV-infected men, the mean CD4+ T cell count was 410 cells/μL, 47.9% were on antiretroviral therapy, and 69.8% had a detectable HIV plasma viral load. In addition, the HIV-infected men were significantly more likely to be positive for hepatitis B core antibody (65.6% vs. 33.0%, $P < 0.01$), HSV type 1 antibody (65.4% vs. 47.9%, $P < 0.01$), and HSV type 2 antibody (39.1% vs. 16.6%) than HIV-uninfected men (Table 1).

Of the 400 samples, 386 (96.5%) swabs (192 from HIV-infected and 194 from HIV-uninfected persons) had adequate β-globin for HPV genotype testing. Overall, 171 (44.3%) of participants had single or multiple HPVs detected. One hundred forty-three participants (37.0%) had at least one of the nHPV

**TABLE 1.** Characteristics of Participants, Bangkok MSM Cohort Study, 2006–2010

| | All Participants (n = 386) | HIV-Infected Participants (n = 192) | HIV-Uninfected Participants (n = 194) | *P* |
|---|---|---|---|---|
| Demographics and risk behavior | | | | |
| Age, mean (SD), y | 25.6 ± 6.2 | 25.8 ± 5.9 | 25.5 ± 6.4 | 0.73 |
| High school education or greater | 343 (88.9%) | 177 (91.2%) | 166 (86.5%) | 0.13 |
| Alcohol ≥1/wk in last 4 mo | 78 (20.2%) | 41 (21.4%) | 37 (19.1%) | 0.57 |
| Drug use in last 4 mo | 164 (42.5%) | 69 (35.6%) | 95 (49.5%) | <0.01 |
| Serologic status of other infections | | | | |
| HSV type 1 antibody | 218 (56.5%) | 125 (65.1%) | 93 (47.9%) | <0.01 |
| HSV type 2 antibody | 107 (27.7%) | 75 (39.1%) | 32 (16.5%) | <0.01 |
| Hepatitis B surface antibody | 153 (39.6%) | 82 (42.7%) | 71 (36.6%) | 0.22 |
| Hepatitis B core antibody | 190 (49.2%) | 126 (65.6%) | 64 (33.0%) | <0.01 |
| Hepatitis B surface antigen | 42 (10.9%) | 26 (13.5%) | 16 (8.2%) | 0.09 |
| Hepatitis A antibody | 92 (23.8%) | 45 (23.4%) | 47 (24.2%) | 0.81 |
| HIV characteristics | | | | |
| CD4 T cell count, mean (SD), cells/μL | NA | 409.8 ± 177.1 | NA | NA |
| Antiretroviral therapy at sampling | NA | 92 (47.9%) | NA | NA |
| HIV RNA | | | | |
| Undetectable | NA | 58 (30.2%) | NA | NA |
| HIV < 100,000, copies/mL | NA | 98 (51.0)% | NA | |
| HIV > 100,000, copies/mL | NA | 36 (18.8%) | NA | |
| HPV type prevalence | | | | |
| HPV6 | 13 (3.4%) | 9 (4.7%) | 4 (2.1%) | 0.15 |
| HPV11 | 60 (15.5%) | 40 (20.8%) | 20 (10.3%) | <0.01 |
| HPV16 | 51 (13.2%) | 32 (16.7%) | 19 (9.8%) | 0.04 |
| HPV18 | 22 (5.7%) | 18 (9.4%) | 4 (2.1%) | <0.01 |
| qHPV (6, 11, 16, or 18) | 126 (32.6%) | 81 (42.2%) | 45 (23.2%) | <0.01 |
| HPV31 | 2 (0.5%) | 1 (0.5%) | 1 (0.5%) | 0.99 |
| HPV33 | 13 (3.4%) | 11 (5.7%) | 2 (1.0%) | 0.01 |
| HPV45 | 16 (4.1%) | 12 (6.3%) | 4 (2.1%) | 0.04 |
| HPV52 | 6 (1.6%) | 4 (2.1%) | 2 (1.0%) | 0.40 |
| HPV58 | 4 (1.0%) | 3 (1.6%) | 1 (0.5%) | 0.31 |
| nHPV (6, 11, 16, 18, 31, 33, 45, 52, or 58) | 143 (37.0%) | 96 (50.0%) | 47 (24.2%) | <0.01 |

All numbers reported in Table 1 represent the column percentages, except for age and CD4 count (which are mean ± SD). For example, 88.9% of all participants have at least a high school education.

qHPV indicates HPV types 6, 11, 16, or 18; nHPV, HPV types 6, 11, 16, 18, 31, 33, 45, 52, or 58.

**TABLE 2.** Prevalence of HPV by Demographic and Lifestyle Characteristics, Bangkok MSM Cohort Study, 2006–2010

| | HIV-Infected Participants | | | HIV-Uninfected Participants | | |
|---|---|---|---|---|---|---|
| | n | % With qHPV | % With nHPV | n | % With qHPV | % With nHPV |
| Overall | 192 | 81 (42.2%) | 96 (50.0%) | 194 | 45 (23.2%) | 47 (24.2%) |
| Age group | | | | | | |
| <22 | 45 | 18 (40.0%) | 22 (48.9%) | 63 | 13 (20.6%) | 13 (20.6%) |
| 22–26 | 75 | 35 (46.7%) | 40 (53.3%) | 65 | 19 (29.2%) | 20 (30.7%) |
| >26 | 72 | 28 (38.9%) | 34 (47.2%) | 66 | 13 (19.7%) | 14 (21.2%) |
| Alcohol use | | | | | | |
| <1/wk | 151 | 64 (42.4%) | 74 (49.0%) | 157 | 36 (22.9%) | 38 (24.2%) |
| ≥1/wk | 41 | 17 (41.5%) | 22 (53.7%) | 37 | 9 (24.3%) | 9 (24.3%) |
| Drug use | | | | | | |
| No | 97 | 44 (45.4%) | 52 (53.6%) | 125 | 26 (20.8%) | 28 (22.4%) |
| Yes | 95 | 37 (39.0%) | 44 (46.3%) | 69 | 19 (27.5%) | 19 (27.5%) |

All numbers reported in Table 2 represent the row percentages. For example, 40.0% of HIV-infected participants in the age <22-year group have at least one of the qHPV types.

qHPV indicates HPV types 6, 11, 16, or 18; nHPV, HPV types 6, 11, 16, 18, 31, 33, 45, 52, or 58.

types; 126 patients (32.6%) had at least one of the qHPV types. Among HPV types identified, the most common genotype was HPV11 (15.5% prevalence), followed by HPV16 (13.2%), HPV18 (5.7%), and HPV45 (4.1%).

Prevalence of qHPV and nHPV virus types was higher among HIV-infected men (Table 1). Individual HPV types HPV11 (20.8% vs. 10.3%, $P < 0.01$), HPV16 (16.7% vs. 9.8%, $P = 0.04$), HPV18 (9.4% vs. 2.1%, $P < 0.01$), HPV33 (5.7% vs. 1.0%, $P < 0.01$), and HPV45 (6.3% vs. 2.1%, $P = 0.04$) were significantly more prevalent in HIV-infected than in HIV-uninfected men. There was a significant difference in both qHPV types (42.2% vs. 23.2%, $P < 0.01$) and nHPV types (50.0% vs. 24.2%, $P < 0.01$) between HIV-infected men and uninfected men.

Prevalence statistics of qHPV and nHPV virus types in different groups by age, alcohol use, and drug use are shown in Table 2. Both qHPV and nHPV virus types were most common in participants' age 22 to 26 years, but there were no statistically significant differences in HPV prevalence across age groups. Increased alcohol consumption was not associated with greater prevalence of qHPV, nor was injectable drug use in either HIV subgroup. Prevalence of qHPV and nHPV virus types also did not vary significantly by employment status or living situation (data not shown).

Prevalence of each HPV virus type according to other concomitant infectious conditions is shown in Table 3. Generally, concomitant infectious diseases (hepatitis A, hepatitis B, HSV types 1 and 2) did not seem strongly associated with qHPV and nHPV type prevalence in either HIV-infected or HIV-uninfected participants. The prevalence of qHPV was not higher in individuals with any of the concomitant infections than it was in the overall study cohort; the same was true for nHPV types.

Table 4 shows the prevalence of anal HPV by self-reported sexual positioning. Notably, there was no significant relationship between sexual positioning and prevalence of qHPV or nHPV types. There were also no significant relationships when testing for relationships between other sexual behaviors (i.e., sexual partners and frequency of condom usage) and HPV prevalence (data not shown).

Among HIV-infected participants, lower CD4+ T cell count (<200 cells/mm$^3$) was associated with a higher prevalence of vaccine-preventable HPV types (Table 5), although this association was not statistically significant ($P = 0.22$). There was no association between HIV plasma ribonucleic acid (RNA) quantification and prevalence of qHPV or nHPV types.

## DISCUSSION

Anal vaccine type HPV is prevalent in this population of Thai MSM. Although it should be acknowledged that testing was done on a convenience sample of swab specimens from the Bangkok MSM Cohort Study and may not be generalizable to the larger population of MSM in Bangkok, the overall rates and distribution by HIV serostatus are comparable to both Western populations and to findings from a previous study in Bangkok.[11,12]

**TABLE 3.** Prevalence of HPV by Prevalence of HPV by Serostatus of Other Infections That May Be Transmitted Through Sex, Bangkok MSM Cohort Study, 2006–2010

| | HIV-Infected Participants | | | HIV-Uninfected Participants | | |
|---|---|---|---|---|---|---|
| | n | % With qHPV | % With nHPV | n | % With qHPV | % With nHPV |
| Overall | 192 | 81 (42.2%) | 96 (50.0%) | 194 | 45 (23.2%) | 47 (24.2%) |
| Seropositivity | | | | | | |
| HSV type 1 | 125 | 55 (44.0%) | 63 (50.4%) | 93 | 23 (22.8%) | 22 (23.7%) |
| HSV type 2 | 75 | 33 (44.0%) | 37 (49.3%) | 32 | 37 (23.0%) | 8 (25.0%) |
| AntiHBS | 82 | 31 (37.8%) | 37 (45.1%) | 71 | 24 (19.5%) | 23 (32.4%) |
| AntiHBC | 126 | 52 (41.3%) | 61 (48.4%) | 64 | 27 (20.8%) | 18 (28.1%) |
| HBSAg | 26 | 9 (34.6%) | 11 (42.3%) | 16 | 43 (24.2%) | 2 (12.5%) |
| AntiHAV | 45 | 14 (31.1%) | 17 (37.8%) | 47 | 8 (17.0%) | 8 (17.0%) |

All numbers reported in Table 3 represent the row percentages. For example, 44.0% of HIV-infected participants with HSV1 have at least one of the qHPV types.

AntiHBS indicates hepatitis B surface antibody; AntiHBC, hepatitis B core antibody; HBSAg, hepatitis B surface antigen; AntiHAV, hepatitis A antibody; qHPV, HPV types 6, 11, 16, or 18; nHPV, HPV types 6, 11, 16, 18, 31, 33, 45, 52, or 58.

**TABLE 4.** Sexual Behavior of Those Infected With Anal HPV Types, Bangkok MSM Cohort Study, 2006–2010

| | HIV-Infected Participants | | | HIV-Uninfected Participants | | |
|---|---|---|---|---|---|---|
| | n | % With qHPV | % With nHPV | n | % With qHPV | % With nHPV |
| Overall | 192 | 81 (42.2%) | 96 (50.0%) | 194 | 45 (23.2%) | 47 (24.2%) |
| Sexual positioning | | | | | | |
| Unknown | 28 | 10 (35.7%) | 12 (42.9%) | 16 | 3 (18.8%) | 3 (18.8%) |
| I | 23 | 10 (43.5%) | 11 (47.8%) | 38 | 6 (15.8%) | 8 (21.1%) |
| R | 44 | 20 (45.5%) | 22 (50.0%) | 40 | 9 (22.5%) | 9 (22.5%) |
| I/R | 74 | 31 (41.9%) | 39 (52.7%) | 72 | 23 (31.9%) | 23 (31.9%) |
| Never anal sex | 23 | 10 (43.5%) | 12 (52.2%) | 28 | 4 (14.3%) | 4 (14.3%) |

qHPV indicates HPV types 6, 11, 16, or 18; nHPV, HPV types 6, 11, 16, 18, 31, 33, 45, 52, or 58; R, receptive; I, insertive.

Although HIV-infected men were more likely to have serological evidence of natural infection with hepatitis B, in addition to infection with both HSV types 1 and 2, they were no more likely to have prevalent anal HPV infection than the HIV-uninfected men. The prevalence of these coinfections suggests increased sexual activity in this group, but this was not borne out in the detailed risk behavior information collected from this cohort and may indicate previous and not ongoing risk.

A higher prevalence of anal HPV with lower CD4+ T cell counts has previously been reported, and although there was a trend in this study, it did not reach statistical significance.[17] Lower CD4+ T cell counts are a marker of progressive immunodeficiency in untreated HIV infection. A higher anal HPV prevalence may therefore be explained by decreased cell-mediated mucosal immunity and its inability to control new, persistent, or recurrent HPV infection. The introduction of combination antiretroviral treatment (CART) in Thailand coincided with the initiation of the current study in 2006. Although the number of CD4+ T cells has been shown to increase incrementally after the initiation of CART, plasma HIV RNA usually declines quickly and becomes undetectable. This temporal difference between these 2 markers in responding to CART may, to some extent, explain the lack of consistency in their reported associations with HPV prevalence.

Similar to findings from the EXPLORE study,[18] where HPV prevalence was evenly distributed over a wide age range, there was no statistically significant difference in the age ranges examined, although HPV types were more commonly seen at a younger age in our population. Anal HPV is often rapidly acquired after sexual debut and thereafter becomes undetectable over a period, which in HIV-infected MSM is reported to approximate 3 years for qHPV types.[19] The higher HPV prevalence in the 22- to 26-year age group likely reflects continued HPV exposure and infection after sexual debut.

**TABLE 5.** Prevalence of HPV by HIV Characteristics Among HIV-infected Participants, Bangkok MSM Cohort Study, 2006–2010

| | n | % With qHPV | % With nHPV |
|---|---|---|---|
| All HIV-infected | 192 | 81 (42.2%) | 96 (50.0%) |
| CD4 T-cell count | | | |
| ≤200 | 18 | 10 (55.6%) | 12 (66.7%) |
| >200 | 174 | 71 (40.8%) | 84 (48.3%) |
| HIV RNA per μL | | | |
| Undetectable | 58 | 24 (41.4%) | 27 (46.6%) |
| <100,000 copes | 98 | 42 (42.9%) | 51 (52.0%) |
| ≥100,000 copies | 36 | 15 (41.7%) | 18 (50.0%) |
| Current ARV therapy | | | |
| Yes | 100 | 42 (42.0%) | 47 (47.0%) |
| No | 92 | 39 (42.4%) | 49 (53.3%) |

ARV indicates antiretroviral; qHPV, HPV types 6, 11, 16, or 18; nHPV, HPV types 6, 11, 16, 18, 31, 33, 45, 52, or 58.

The lack of association between social behaviors (alcohol and drug use), sexual behaviors (condom usage, sexual partners, and sexual positioning), and HPV prevalence is surprising, but may be explained by the biases associated with conducting a selective population study such as this one. We cannot assume that the reported behaviors accurately reflect the lifetime exposure to risk behaviors such as alcohol, drug use, and sexual behavior that could result in acquisition of sexually transmitted infections.

The prevalence of qHPV and nHPV types in both HIV serostatus groups indicates that Thai MSM would benefit from targeted HPV vaccination in a similar way to Western MSM. This would not only prevent anal HPV if given before exposure but also reduce the incidence of sequelae such as warts, dysplasia, and anogenital cancers. Furthermore, there is also evidence that HPV vaccination may protect against HPV types, most commonly HPV16, that are found in the oropharynx and are associated with cancer at this site.[20] And finally, because anal HPV infection may be a risk for incident HIV in MSM, vaccination could have the potential to mitigate this risk.[21]

Human papillomavirus vaccination is one example of an available intervention for MSM. However, a broader concern relates to addressing how access to comprehensive strategies that may include HPV, and multiple other vaccines can be developed and implemented to reduce the overall level of morbidity and mortality in this vulnerable population.

## REFERENCES


1. Chesson HW, Ekwueme DU, Saraiya M, et al. The cost-effectiveness of male HPV vaccination in the United States. Vaccine 2011; 29: 8443–8450.
2. Daling JR, Weiss NS, Klopfenstein LL, et al. Correlates of homosexual behavior and the incidence of anal cancer. JAMA 1982; 247:1988–1990.
3. Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis 2012; 54:1026–1034.
4. Bosch FX, Broker TR, Forman D, et al. Comprehensive control of human papillomavirus infections and related diseases. Vaccine 2013; 31(suppl 7):H1–H31.
5. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007; 356:1928–1943.
6. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011; 365:1576–1585.
7. Van Aar F, Mooij SH, van der Sande MA, et al. Anal and penile high-risk human papillomavirus prevalence in HIV-negative and HIV-infected MSM. AIDS 2013; 27:2921–2931.
8. Glick SN, Feng Q, Popov V, et al. High rates of incident and prevalent anal human papillomavirus infection among young men who have sex with men. J Infect Dis 2014; 209:369–376.
9. Torres M, González C, del Romero J, et al. Anal human papillomavirus genotype distribution in HIV-infected men who have sex with men by

geographical origin, age, and cytological status in a Spanish cohort. J Clin Microbiol 2013; 51:3512–3520.
10. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: A systematic review and meta-analysis. Lancet Oncol 2012; 13:487–500.
11. Palefsky JM, Holly EA, Ralston ML, et al. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)–positive and HIV-negative homosexual men. J Infect Dis 1998; 177:361–367.
12. Phanuphak N, Teeratakulpisarn N, Pankam T, et al. Anal human papillomavirus infection among Thai men who have sex with men with and without HIV infection: Prevalence, incidence, and persistence. J Acquir Immune Defic Syndr 2013; 63:472–479.
13. van Griensven F, Thienkrua W, McNicholl J, et al. Evidence of an explosive epidemic of HIV infection in a cohort of men who have sex with men in Thailand. AIDS 2013; 27:825–832.
14. Holtz TH, Pattanasin S, Chonwattana W, et al. Longitudinal analysis of key HIV-risk behavior patterns and predictors in men who have sex with men, Bangkok, Thailand. Arch Sex Behav 2015; 44:341–348.
15. Schmitz M, Scheungraber C, Herrmann J, et al. Quantitative multiplex PCR assay for the detection of the seven clinically most relevant high-risk HPV types. J Clin Virol 2009; 44:302–307.
16. van den Brule AJ, Pol R, Fransen-Daalmeijer N, et al. GP5+/6+ PCR followed by reverse line blot analysis enables rapid and high-throughput identification of human papillomavirus genotypes. J Clin Microbiol 2002; 40:779–787.
17. Palefsky JM Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus–positive men and women. J Natl Cancer Inst Monogr 1998:15–20.
18. Chin-Hong PV, Vittinghoff E, Cranston RD, et al. Age-specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: The EXPLORE study. J Infect Dis 2004; 190:2070–2076.
19. de Pokomandy A, Rouleau D, Ghattas G, et al. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: The HIPVIRG cohort study. J Infect Dis 2009; 199:965–973.
20. Herrero R, Quint W, Hildesheim A, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS One 2013; 8:e68329.
21. Chin-Hong PV, Husnik M, Cranston RD, et al. Anal human papillomavirus infection is associated with HIV acquisition in men who have sex with men. AIDS 2009; 23:1135–1142.