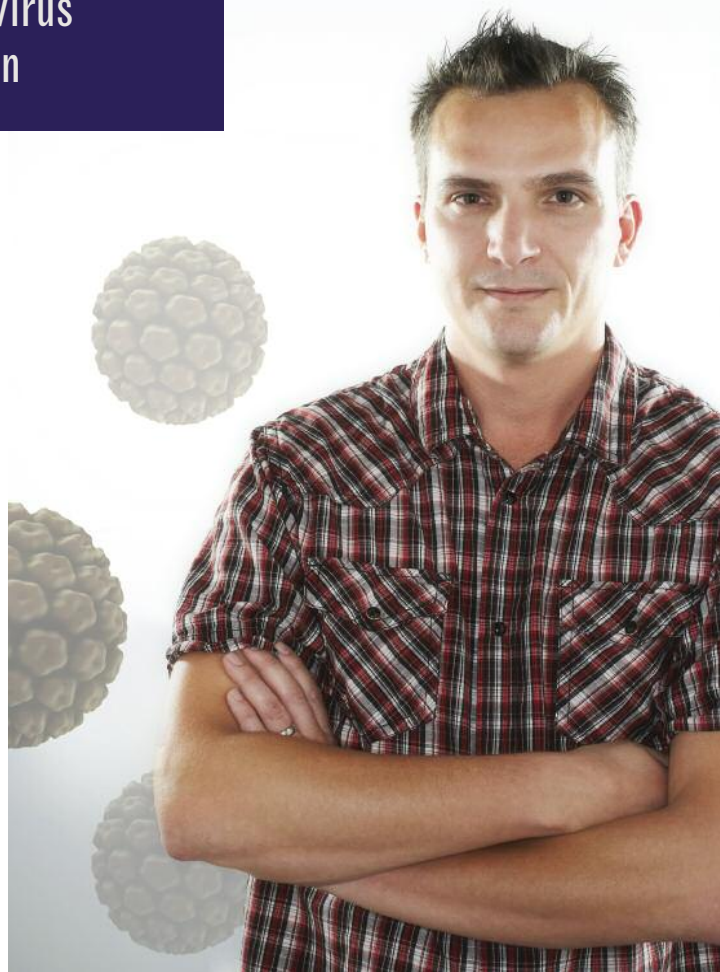


Genital, Oral, and Anal Human Papillomavirus Infection in Men Who Have Sex With Men

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Even though the incidence of anal cancer among men who have sex with men (MSM) is higher than the incidence of cervical cancer among women, few MSM are identified as high-risk patients in primary care or have received vaccination for human papillomavirus (HPV), the most common sexually transmitted infection worldwide, with 6.2 million new infections each year. The authors review the current literature on diagnosis and basic management of genital, oral, and anal HPV infection. Early diagnosis and treatment of patients with HPV infection is important because this infection causes patients substantial distress even in its benign manifestations. It has also been implicated in a host of cancers, including oral, cervical, penile, and anal cancers and is an independent risk factor for the development of human immunodeficiency virus infection. The incidence of HPV infection drops in women older than 30 years but remains high for MSM in all age ranges. For all of these reasons, physicians should routinely assess the sexual practices of all male patients, especially MSM, and educate them on the HPV infection risks, diagnosis, and treatment options. Physicians can have a significant impact in the primary prevention of HPV by routinely offering HPV vaccination to male patients younger than 26 years.

J Am Osteopath Assoc. 2011;111(3 suppl 2):S19-S25



A major milestone in medicine occurred in 2006 when the Food and Drug Administration approved the first vaccine against human papillomavirus (HPV).¹ In 2009, the Food and Drug Administration subsequently licensed the quadrivalent HPV vaccine for use in boys and young men aged 9 to 26 years.² Although the vaccine was initially indicated for young women,

HPV infection is highly prevalent in males and is responsible for substantial disease in men, particularly men who have sex with men (MSM).^{3,4} For example, HPV infection is an independent risk factor for acquiring human immunodeficiency virus (HIV) infection and some forms of cancer.^{5,6} In one study, a majority of the MSM surveyed admitted to having genital warts but did not think they had an HPV infection.⁷

Men who have sex with men may be difficult to identify in general practice because many of them do not self-identify as gay or bisexual or are still having sex with women as they develop their sexual identity.⁸ Studies indicate

that prior estimates of the MSM population were too low and that physicians in general practice can anticipate that 3% of their male patients have had sexual contact with another man in the previous year.^{9,10} One study¹¹ found that 15% of men in a random sample reported some type of sexual contact with another man, irrespective of how they self-identified their sexuality.

In this article we will review the prevalence and basic management of the most common manifestations of HPV infection in MSM, including genital, penile, oral, and anal HPV infection. We will also discuss the possible benefits of offering the HPV vaccine to MSM for the primary prevention of anal carcinoma

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Financial Disclosures: None reported.

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This supplement is supported by an independent educational grant from Merck & Co, Inc.

and HPV transmission to men or women and to reduce the risk of HIV infection.

General Population

The Centers for Disease Control and Prevention (CDC) estimates that 20 million individuals are infected with HPV. This number grows larger as 6.2 million new individuals are infected each year, making HPV infection the most common sexually transmitted viral infection worldwide.^{12,13} The prevalence of the virus tends to peak after a patient's first sexual encounter (ie, "sexual debut") and remains high with each new sexual partner among all age groups.^{14,15} The risk of developing anal cancer is 17 times higher in gay or bisexual men than in heterosexual men.^{3,16} A 2008 meta-analysis of the current literature found that HPV is associated with 85% of anal squamous cell carcinomas in men, 50% of penile cancers, and up to 72% of oropharyngeal cancers.⁶ Cancers associated with HPV infection are mostly due to HPV-16 or HPV-18, with numbers roughly approximating the number of cervical cancers in the United States.¹⁷ These findings are particularly worrisome for MSM, because oral sex, anal receptive intercourse, and noninsertive, "safe sex" contact can all result in HPV transmission.¹⁸

Genital and Penile Condylomas Caused by HPV-6 or HPV-11

Epidemiology

The CDC reports that only 1% of sexually active men have visible genital warts at any given time, yet if advanced antibody testing methods are used, up to 73% of healthy men have detectable HPV in the external genital tract.^{6,16} Genital warts (condyloma acuminatum, venereal warts) are a common symptom of infection with HPV-6 or HPV-11.²⁰ Even though condyloma-associated HPV strains 6 and 11 are considered low risk because of their nononcogenic nature, they are still transmissible, incur costs of frequent treatment, and have emotional costs to patients.¹⁹ Both HPV-6 and HPV-11 can cause recurrent respiratory papillomatosis, an uncommon condition in which condylomas develop in the throat, potentially blocking the patient's airway.^{6,12}



Figure 1. Genital condyloma on a scrotum. Reprinted with permission from John C. Hall, MD.

History and Diagnosis

Most genital HPV infection is transmitted by skin-to-skin sexual contact usually involving friction or micro-trauma to exposed skin.²⁰ Subclinical infections are common; exophytic or visible condylomas usually appear 1 to 3 months after exposure but can appear much later.²⁰ There is no standard method to diagnose genital HPV other than visual inspection and clinician experience. Biopsies are usually not necessary, and HPV DNA sampling is usually not available or practical.^{3,20} Generally, genital warts are painless, flesh-colored or pale-pink lesions with cauliflower, velvety, or smooth textures (Figure 1). Single lesions can be present anywhere on the penile shaft, urethra, scrotum, or perineum and can be symmetric on opposing moist surfaces. Individual condylomas may coalesce in large masses around the penis or perineal area, including the anus.^{20,21} For confusing or subclinical lesions, a 5% solution of acetic acid (acetowhite test) can be applied to reveal or whiten incon-

spicuous lesions, but this is a nonspecific technique and its positive and negative predictive values are unknown.^{3,21}

Lesions can be confused for other conditions, such as pearly penile papules, molluscum contagiosum, or bowenoid papulosis lesions (Figure 2), and invasive precancerous lesions.²⁰ Questionable, atypical, or treatment-resistant lesions should be examined with biopsy for definitive diagnosis. Penile carcinoma is rare but is highly associated with the presence of HPV-16 and the state of being uncircumcised.⁴ Patients who are MSM with newly diagnosed condylomas should be screened for other sexually transmitted diseases including HIV infection, hepatitis C virus infection, chlamydia, and gonorrhea.

Treatment

There are a variety of patient- and physician-applied treatments for condylomas, though no treatment is 100% effective.



Figure 2. Penile bowenoid papulosis lesions. Such lesions can be mistaken for genital condyloma. Reprinted with permission from John C. Hall, MD.

First-line treatments, such as podofilox 0.5% solution or imiquimod 5%, applied directly to the condyloma, are generally safe and convenient for self-application to clinically visible lesions^{20,22} (Figure 3). Physician-applied treatments, such as cryotherapy, podophyllin 20% resin, trichloroacetic acid, and surgical removal are more effective but may also need to be repeated after 1 to 2 weeks^{4,22} and require training by the treating physi-

cian (Figure 4 and Figure 5). Lesions that do not respond to basic therapy or are so extensive that they cause the patient substantial physical or emotion distress should be referred to a specialist for surgery, carbon dioxide laser treatment, or advanced immune-modulating therapies, such as interferon α 2b or 5-fluorouracil.²¹ The response rates for cryotherapy range from approximately 60% to 90%, compared with 0% to 50% for placebo^{24,25} (Table).

Oral HPV Epidemiology

Men who have sex with men have a high risk of developing oral HPV infection. A 2009 study²⁶ found that oral HPV acquisition was more positively associated with number of recent oral sex and open mouth kissing partners than with the number of vaginal sex partners. Additionally, the prevalence of oral condylomas has increased dramatically since the introduction of highly active antiretroviral therapy among HIV-positive patients, which may be due to immune reconstitution.²⁷ Human papillomavirus not only causes oral condylomas but is also strongly associated with oropharyngeal cancers and other oral diseases.^{28,29} Oral squamous cell carcinoma is the eighth most common cancer in men, and HPV is linked to at least 25% of the cases.^{30,31} The incidence of HPV-associated carcinomas of the oropharynx substantially increased from 1973 to 2004 (annual percentage change, 80%; $P < .001$), most likely because of a shift in sexual behaviors, particularly oral sex in young males.^{31,32}

Common noncancerous oral lesions associated with HPV include oral condylomas (Figure 6), oral leukoplakia (Figure 7), and oral lichen planus.²⁹ Condyloma lesions appear as white or pink sessile, flat, raised, or cauliflowerlike nodules on the mucous membranes or tongue.²¹ The most commonly found HPV types are 6, 11, 16, and 18.²¹ Oropharyngeal cancers due to HPV occur more commonly among men than among women and account for a large proportion of HPV-associated cancers, second to cervical cancer.³³

| Treatment | Mechanisms of Action |
|---------------------------------------|--|
| Cryotherapy | Destruction by thermal-induced cytolysis |
| Imiquimod (Aldara) | Cell-mediated immune response modifier; induces interferon production |
| Interferon | Antiviral, antiproliferative, and immunomodulatory activity |
| Podofilox (Condylox; solution or gel) | Cytotoxic, antimitotic; major biologically active component of podophyllin resin |
| Podophyllin resin | Cytotoxic, antimitotic (causes tissue necrosis) |
| Trichloroacetic acid | Protein coagulation of condyloma tissue |

Figure 3. Mechanisms of selected treatment options for genital warts. Reprinted with permission from Kodner and Nasraty.²³

| Treatment | Typical Cycle |
|---|--|
| ■ Patient-Applied | |
| □ Imiquimod (Aldara) | Apply at bedtime for 3 days, then rest 4 days; alternatively, may apply every other day for 3 applications; may repeat weekly cycles up to 16 weeks. |
| □ Podofilox (Condylox; solution or gel) | Apply twice daily for 3 days, then rest 4 days; may repeat for 4 cycles. |
| ■ Physician-Applied | |
| □ Cryotherapy | Use liquid nitrogen or cryoprobe; may be repeated every 1 to 2 weeks, if necessary. |
| □ Interferon | Not recommended for office use. |
| □ Podophyllin resin | Apply to each condyloma and allow to dry; may be repeated weekly, if necessary. |
| □ Trichloroacetic acid | Apply a small amount to visible condylomas and allow to dry; may be repeated weekly, if necessary. |

Figure 4. Typical treatment cycles for patients with genital warts. Reprinted with permission from Kodner and Nasraty.²³

Treatment

Oral condyloma treatment is similar to treatment of lesions in other areas of the body where mucosal surfaces are involved. Cryotherapy, surgical excision, laser treatment and topical 5-fluorouracil are common treatments but should be used by physicians or dentists experienced with their use in this area.^{20,27} Ablation of condylomas does reduce transmission,²² but there is no known way to completely prevent their spread to sexual partners.

Anal HPV Epidemiology

Large multicenter studies have shown that 57% of HIV-negative MSM have

anal HPV infection, with 26% of them having a high-risk strain.³⁴ This prevalence persists for MSM across all age groups, whereas the incidence of HPV infection in women tends to peak when women are aged in their late 20s and again after age 55 years.³⁴ Even though most HPV infections are transient, MSM have more sexual partners, more new sexual partners, and therefore more new exposures to HPV infection after age 30 years than most women.^{15,32} HPV-16, one of the types associated with anal neoplasms, is the most common strain found in anal HPV infections among MSM.^{18,35}

HPV-Associated Carcinoma

The incidence of anal cancer among

■ Patient-Applied

- Podofilox 0.5% solution or gel. Podofilox solution should be applied with a cotton swab, or podofilox gel with a finger, to visible genital condylomas twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to 4 cycles. The total condyloma area treated should not exceed 10 cm², and the total volume of podofilox should be limited to 0.5 mL/d. If possible, the healthcare provider should apply the initial treatment to demonstrate the proper application technique and identify which condylomas should be treated. The safety of podofilox during pregnancy has not been established.
- Imiquimod 5% cream. Imiquimod cream should be applied once daily at bedtime, 3 times a week for up to 16 weeks. The treatment area should be washed with soap and water 6-10 hours after the application. The safety of Imiquimod during pregnancy has not been established.
- Sinecatechins 15% ointment. This ointment should be applied 3 times daily (0.5 cm strand of ointment to each condyloma) using a finger to ensure coverage with a thin layer of ointment until complete clearance of condylomas. This product should not be continued longer than 16 weeks. The medication should not be washed off after use. Sexual contact should be avoided while the ointment is on the skin.

■ Provider-Administered

- Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1-2 weeks.
- Podophyllin resin 10%-25% should be applied to each condyloma and allowed to air dry before the treated area comes into contact with clothing; over application or failure to air dry can result in local irritation caused by spread of the compound to adjacent areas. The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, the following 2 guidelines should be followed: (1) application should be limited to <0.5 mL of podophyllin or an area of <10 cm² of condylomas per session and (2) the area to which treatment is administered should not contain any open lesions or wounds. The preparation should be thoroughly washed off 1-4 hours after application to reduce local irritation. The safety of podophyllin during pregnancy has not been established.
- Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%-90%. TCA solutions have a low viscosity comparable with that of water and can spread rapidly if applied excessively; therefore, they can damage adjacent tissue. A small amount should be applied only to the condylomas and allowed to dry before the patient sits or stands, at which time a white frosting develops. If pain is intense, the acid can be neutralized with soap or sodium bicarbonate. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.
- Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrocautery

■ Alternative Regimens

- Intra-lesional interferon
- Laser surgery

Figure 5. Regimens recommended by the Centers for Disease Control and Prevention for the management of external genital warts.²²

MSM is higher than cervical cancer rates among women.^{15,34} The latter tend to fall substantially after age 30 years, but MSM are at risk for HPV-associated anal squamous cell intraepithelial lesions throughout their lives in all age groups.¹⁵ Human papillomavirus has been definitively associated with more than 85% of all cancerous or precancerous anal lesions worldwide.^{35,36}

Diagnosis and Management

Condylomas associated with HPV infection can be external or internal, making many lesions difficult to visualize. Patients often report noticing the condylomas after defecation or during sex, particularly if the lesions are in the anal canal, which extends about 3 cm from the anal verge to the anorectal transition zone³⁷ (Figure 8). Exophytic condylomas can be managed similarly to other genital warts by using patient- and physician-

applied topical treatments, as discussed elsewhere³⁸ (Figures 3 through Figure 5; Table). The treatment algorithm becomes more complicated with evaluation for the presence of HPV-16 infection, HPV-18 infection, or anal dysplasia.

Anal Papanicolaou tests are increasingly being used to diagnose neoplastic lesions with the same sampling techniques used for cervical Papanicolaou tests.³⁸ Studies are underway to determine standard guidelines for interpreting anal cytologic findings, but abnormal cells can be easily identified with typical cervical cytology interpretation practices.⁴ Patients with abnormal anal cytologic findings should be referred for high-resolution anoscopy, performed by a specialist trained in its use; high-resolution endoscopy, or *anal colposcopy*, is an effective way to identify, sample for biopsy, and manage early neoplastic lesions or identify patients who need referral to a colorectal surgeon for management.³⁸

The HPV-HIV Link

Physicians who care for MSM should be aware that HPV infection is an independent risk factor for the subsequent development of HIV infection.⁵ Patients presenting with HPV infection in any of its forms should be screened for HIV infection at the office visit, preferably with a rapid finger stick or rapid oral HIV test.⁵ Higher HIV infection rates are seen among patients already infected with HPV.⁵ This association is believed to occur through 2 distinct mechanisms. One mechanism is that sexually transmitted infections such as HPV disrupt normal mucosal anatomic barriers and may allow HIV-infected body fluids direct access to open or bleeding lesions. Another proposed mechanism is that CD4+ T cells and macrophages are recruited in higher numbers to skin surfaces infected with HPV, allowing closer potential contact between HIV-infected fluids and host CD4+ T cells.⁵

HPV Vaccine and Men

Men infected with HPV serve as vectors for the spread of the virus to both men and women.¹⁹ It has been demonstrated in recent meta-analyses^{36,39,40} that the cur-

Table.
Comparison of Treatments for Patients With Genital Warts

| Treatment | Cost by Condyloma Type ^{11*} | Adverse Effects and Their Incidence (%) [†] | Clearance Rate, % ^{9,12} | Risk of Recurrence, % ^{9,10,12-14‡} |
|----------------------------|---------------------------------------|--|-----------------------------------|--|
| Cryotherapy | Simple: \$268 Extensive: \$415 | Pain or blisters at application site (20) | 60-90 | 20-40 |
| Imiquimod (Aldara) | Simple: \$607 Extensive: \$649 | Erythema (70); irritation, ulceration, and pain (<10); burning, erosion, flaking, edema, induration, and pigmentary changes at application site; minimal systemic absorption | 30-50 | 15 |
| Interferon (intralesional) | Simple: \$2744 Extensive: \$5803 | Burning, itching, and irritation at injection site; systemic myalgias, headaches, fever, chills, leukopenia, elevated transaminase levels (6), thrombocytopenia (1) | 20-60 | NA |
| Laser | Simple: \$197 Extensive: \$535 | Similar to surgical excision; risk for spreading human papillomavirus via smoke plumes | 25-50 | 5-50 |
| Podofilox (Condylox) | Simple: \$200 Extensive: \$334 | Burning at application site (75), pain (50), inflammation (70); low risk for systemic toxicity | 45-80 | 5-30 |
| Podophyllin resin | Simple: \$385 Extensive: \$1449 | Local irritation, erythema, burning, and soreness at application site (75); possibly mutagenicity, oncogenicity | 30-80 | 20-65 |
| Surgical excision | Simple: \$210 Extensive: \$318 | Pain (100), bleeding (40), scarring (10); risk for burning and allergic reaction from local anesthetic | 35-70 | 20 |
| Trichloroacetic acid | Simple: \$513 Extensive: \$966 | Local pain and irritation; no systemic side effects | 50-80 | 35 |
| Placebo | None | NA | 0-55 | NA |

* Cost is per successful treatment course.
† Rates of adverse effects are not compared with rates for placebo.
‡ Recurrence rates are approximated from ranges identified in the referenced texts. Time until recurrence varies across studies, but recurrence rates typically are measured at 3 months after treatment.

Abbreviation: NA, not available.

Source: Reprinted with permission from Kodner and Nasraty.²³

rent HPV vaccine is more than 95% effective against HPV-16 and HPV-18 and could prevent up to 80% of anal carcinomas. The quadrivalent HPV vaccine has also been announced to have 90% efficacy against HPV types 6, 11, 16, and 18 in males aged 16 to 26 years.⁴¹ When an HPV vaccine is approved for males,

physicians should be proactive in offering it to their young male patients and all patients who are MSM.⁴² Even patients who are knowledgeable about HPV and HIV can and do engage in high-risk sexual behaviors,⁴³ and MSM may not ask to be screened for HPV or HIV infection.

As knowledge of the HPV vaccine in US communities grows, MSM are increasingly interested about the possibility of being vaccinated. More than 93% of one surveyed group said they would be willing to disclose their sexual history to receive vaccination.⁴⁴ Other attitude assessments have determined that young



Figure 6. Oral condyloma (A), oral condyloma on the lower lip (B), and external lip condyloma (C). Reprinted with permission from David Reznik, DDS.



Figure 7. Oral hairy leukoplakia. Reprinted with permission from David Reznik, DDS.



Figure 8. Anal condyloma. Reprinted with permission from John C. Hall, MD.

male patients are more willing to be vaccinated if their healthcare provider emphasizes the high prevalence of HPV infection in their communities and the vaccines' threat to their own health more than the patients' risk of transmitting HPV infection to others.⁴⁵ A review of the literature shows that acceptance of the HPV vaccine for males is generally high among physicians and patients, but patient acceptance is highly dependent on physicians' offering the vaccine first.^{19,46}

Historically, physicians have been uncomfortable discussing sexual health issues with patients who are MSM.^{8,47} Young gay males may experiment with their sexuality and maintain sexual relationships with both male and female partners, in essence doubling their risk of exposure to and transmission of HPV infection. Given that about 25% of all

HPV-associated carcinomas occur in men,¹⁷ widespread vaccination of young men is being considered by the CDC Advisory Committee on Immunization Practices.⁴²

Conclusion

With the availability of a vaccine that not only could prevent HPV-associated cancer and other diseases but could also help reduce transmission of HIV,⁵ physicians have an obligation to incorporate sexual health history and vaccinations into the routine care of their male patients.

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