Background and Epidemiology

Background

Human papillomavirus (HPV) is one of the most common sexually transmitted infections (STIs). More than 170 types of HPV have been classified and more than 40 types of HPV can infect the genital tract of humans. Genital HPV types are divided into two groups based on whether they have an association with cancer. Infections with low-risk types (non-oncogenic) are not associated with cancer but can cause genital warts and benign or low-grade cervical cellular changes. Infections with high-risk types (oncogenic), most notably HPV types 16 and 18, can cause low-grade cervical cellular changes, high-grade cervical cellular changes (moderate to severe Pap test abnormalities), and cancer of the cervix; in addition, some high-risk HPV types have been associated with cancers of the vulva, vagina, anus, penis, and oropharynx. Most HPV infections, whether caused by low-risk or high-risk types, are transient, asymptomatic, and have no clinical consequences. Estimates on the incidence and prevalence of HPV infection are limited because HPV infection is not a reportable disease in the United States, precise yearly statistics on the incidence (new HPV infections) are not available. However, the Centers for Disease Control and Prevention (CDC) estimates there are approximately 14.1 million new HPV infections in the United States each year. More information is known regarding HPV prevalence (persons living with HPV infection), particularly based on data from the National Health and Nutrition Examination Survey (NHANES). In the United States, an estimated 79 million women aged 14 to 59 years are infected with HPV, with the highest prevalence among those aged 20 to 24 years. In addition, a substantial number of genitourinary cancers and anogenital warts are attributable to HPV infection. For example, in 2009, an estimated 35,000 new HPV-associated cancers and 355,000 new cases of anogenital warts were associated with HPV infection. In the past decade, genital warts has consistently accounted for 300,000 or more visits to an out-patient health care facility. In a separate analysis, the CDC estimated an average of 30,700 annual cancers attributable to HPV during the years 2008-2012, with approximately 60% of these cancers involving females. Notably, in this CDC analysis, the rates of cervical carcinoma were higher among blacks than among whites, and among Hispanics than non-Hispanics. In addition, higher rates of HPV-associated
cancer were seen among persons living in the southern region of the Unites States compared with those living in other regions.

**Impact of HPV Vaccine on HPV Prevalence**

The prevalence of infection with high-risk types has drastically decreased with the availability of effective HPV vaccines. A recent study analyzed 14 to 34 year-old females in the NHANES study group and compared rates of vaccine-targeted strains between the pre-vaccine era (2003-2006) and 4 years of the vaccine era (2009-2012).[11] This study demonstrated a 64% decrease in vaccine-targeted HPV prevalence among females aged 14 to 19 years and a 34% decrease among those aged 20 to 24 years; there was not a significant decrease in women aged 25 to 29 but only 14.7% had received the HPV vaccine (Figure 2).[12] These findings are somewhat dynamic as the number of types in the HPV vaccine used in the United States has expanded from 4 to 9.[13] Even without the expanded types in the HPV vaccine, the overwhelming trend is towards a decrease in the prevalence of infections by high-risk types of HPV in vaccinated populations.

**Impact of HPV Vaccine on HPV-Related Disease**

The availability of effective HPV vaccines has led to a decline in some but not all sequelae of HPV infections among women in the United States.[10,14] In a meta-analysis of 20 eligible studies, investigators showed that in countries with female vaccination coverage of at least 50%, HPV type 16 and 18 infections decreased by 68% between the pre-vaccination and post-vaccination periods and anogenital warts decreased by 61% in girls 13-19 years of age.[15] In the United States, the prevalence trends for anogenital warts varies by age and sex (Figure 3). [16] Among females aged 15–19, HPV prevalence was stable during 2003–2007, but then significantly declined during 2007–2010.[16] Among females aged 20–24 years, anogenital wart prevalence significantly increased during 2003–2007, was stable during 2007–2010, then began to decrease during 2009–2010.[16] Prevalence in females 25-39 years of age (persons unlikely to have been vaccinated) significantly increased throughout the time period. For males aged 15-39 years, the anogenital wart prevalence for each 5-year age group increased from 2003-2009, but no increases were observed for 2010.[16] Rates of precancerous lesions declined following the introduction of HPV vaccination; an analysis of the New Mexico HPV Pap Registry from 2007-2014 showed significant declines in all stages of cervical intraepithelial neoplasia (CIN) for women aged 15-19 years.[17] Data from the CDC HPV-IMPACT Project, a sentinel surveillance project, also demonstrated dramatic declines in cervical precancer incidence from 2008-2012 for women aged 18-20 years, with some sites also demonstrating significant declines among women aged 21-29 years.[18] Of note, screening recommendations changed during this time period so declines in disease may reflect both reduced screening and impact of vaccination. During the same time there was a significant decline in prevalence of HPV 16- and 18-related precancer among adult women who received at least 1 dose of HPV vaccine.[19]

**Risk Factors**

Key risk factors associated with acquisition of genital HPV infection include higher number of sexual partners and lower education level.[20] Investigators have evaluated potential risk factors associated with cervical cancer, including oral contraceptives, multiple pregnancies, tobacco smoking, nutrition (vitamins C and E, carotenoids, xanthophylls), immunosuppression, prior herpes simplex virus 2 infection, or *Chlamydia trachomatis* infection. These factors may possibly play a secondary role in progression to cervical cancer, but none consistently demonstrate the same strength of association as seen with high-risk HPV infection.

**Cost**

In the United States, direct annual medical costs associated with genital HPV infection, including treatment of genital warts, precancers and cancers, and screening for cervical cancer, are estimated to be $1.7 billion.[5]
Microbiology, Pathogenesis, and Natural History

Virology

Viral Structure

Human papillomavirus is a small, non-enveloped, double-stranded DNA virus that is approximately 55 nm in diameter and a member of the Papillomaviridae family. The viral DNA genome encodes eight open reading frames comprised of six early (E1, E2, E4, E5, E6, E7) proteins that maintain regulatory function (and can cause cell oncotransformation) and two late (L1 and L2) proteins. Human papillomavirus has a characteristic icosahedral viral outer shell, primarily comprised of 360 molecules of the L1 major protein arranged as 72 star-shaped pentameric capsids (Figure 4).[3,22] The L1 protein, which serves as the primary structural element, can spontaneously self-assemble into 72 pentamers, forming a virus-like particle (Figure 5); this self-assembling property is the key element used in design and production of the HPV vaccine.[23] The viral shell also contains up to 72 molecules of the L2 minor protein, but the exact location and function of the L2 minor proteins remain poorly understood.[24]

Classification of HPV Types

The HPV types that infect humans have a known specificity for epithelial sites.[3] Genital HPV types have specific affinity for genital skin and mucosa. The identification and typing of HPV in tissues occurs via the detection of HPV DNA or mRNA. Infection with HPV is characterized by low-risk (non-oncogenic types) and high-risk (oncogenic types) (Table 1).[3,10]

Pathogenesis

HPV infection occurs at the basal cell layer of stratified squamous epithelial cells. Infection stimulates cellular proliferation in the epithelium and infected cells display a broad spectrum of changes, ranging from benign hyperplasia to dysplasia to invasive carcinoma. To effectively replicate, HPV must utilize the host cellular machinery. During the process, the viral protein product encoded by E6 binds to the p53 tumor suppressor gene product, which results in the premature degradation of the p53 protein.[25] The E7 protein binds to a tumor suppressor protein—the retinoblastoma protein—and inhibits its function.[26] These protein products mediate much of the virus’ oncogenic potential and their production represents a key difference between the low- and high-risk strains of HPV.

Transmission of Genital HPV

Transmission of genital HPV is predominantly associated with sexual activity. Although a greater number of lifetime sexual partners is associated with a higher likelihood of acquiring HPV, even a person with a few or even one lifetime sexual partner can get infected. Transmission does not require presence of visible lesions in the source individual and transmission of HPV frequently occurs from persons who are asymptomatic or have subclinical infection. Consistent and correct use of condoms reduces the risk for genital HPV acquisition or transmission, and therefore reduces the risk for HPV-associated diseases (e.g., genital warts and cervical cancer).[27] Condom use does not entirely prevent transmission of HPV, since exposure to HPV can occur in areas that are not covered or protected by a condom (e.g., scrotum, vulva, or perianal region). Treatment of warts or cervical cellular abnormalities will reduce, but may not eliminate the risk of transmission. HPV can be found on fomites (environmental surfaces and objects) but transmission by fomite has never been documented. Although rare, genital HPV infection with low-risk types can be transmitted from mother to newborn during delivery and it may cause respiratory tract warts known as recurrent respiratory papillomatosis (RRP); in children, this condition is called juvenile-onset RRP (JORRP).[28] The value of cesarean delivery to prevent development of JORRP in children to mothers with genital warts is unknown and, thus, should not be performed solely to prevent transmission of genital HPV to the newborn.
Natural History of HPV Infections

Available data suggest that more than 90% of individuals with genital HPV infections are asymptomatic and clear the infection within 2 years.[29] The incubation period, representing the time from acquisition to clinical manifestations, is variable and ranges from 3 weeks to several months for genital warts and several months to years for cervical cellular abnormalities. If cervical cancer develops, it typically occurs decades after the initial infection. Following acquisition of HPV, the median duration of HPV infection of the cervix (measured by detection of HPV DNA) is approximately 1 year.[30] The potential progression to cervical cancer is a dynamic process with a spectrum of potential outcomes that include immune-mediated clearance of HPV from the cervix, progression to a precancerous lesion, regression of precancerous lesions, and progression of precancerous lesions to cervical cancer with invasion of local tissue planes (Figure 6).[31,32,33,34] The frequency of spontaneous regression is unclear; a few studies indicate a regression rate with cervical intraepithelial neoplasia (CIN) 2 of 19% to 40% over 6 months to 2 years.[35,36,37] Available data strongly suggest that persistent HPV infection is essential in the process of oncogenesis. Persistent HPV infection with high-risk HPV types is the most important risk factor for precancerous (high-grade) cervical cellular changes and cervical cancer. Additional factors associated with persistent infection include older age, certain HPV types, and immunodeficiency.
Clinical Manifestations

Overview of HPV-Related Manifestations

Most HPV infections are transient, asymptomatic, or subclinical, and, among immunocompetent individuals, most HPV infections have no clinical consequences. Patients with clinically evident disease have a range of possible presentations that correlate with the HPV type and host factors. The three most common clinically significant manifestations associated with HPV infection are anogenital warts, cervical cellular abnormalities (or lesions that are detected by Pap test or enhanced visual inspection methods), and anal cancer in men who have sex with men. A minority of patients with cellular abnormalities will subsequently progress to cervical cancer, which in an early phase may not be evident on visual inspection, but later may manifest as a cervical irregularity or mass.

Anogenital Warts

Types of Anogenital Warts

Patients with visible anogenital warts frequently are infected simultaneously with multiple HPV types. Anogenital warts have four major morphologic types:

- Condylomata acuminata (cauliflower-like appearance and may be skin-colored, pink, or hyperpigmented)
- Smooth papules (usually dome-shaped and skin-colored)
- Flat papules (macular to slightly raised, skin-colored, and have a smooth surface)
- Keratotic warts (with a thick keratinized layer that can resemble common warts or seborrheic keratoses)

Sites for Anogenital Warts

Anogenital warts commonly occur in areas of coital friction. For men, this includes external warts on the penis, urethral meatus, scrotum, perineum (Figure 7), and perianal area; in addition, men can have internal warts involving the urethral meatus or intra-anal mucosa. For women, external warts can appear on the vulva, vaginal introitus, perineum, and perianal area; women can develop internal warts on the vagina, cervix (Figure 8), and anal mucosa. Perianal warts do not necessarily imply anal intercourse, but may be secondary to autoinoculation, sexual activity other than intercourse, or spread from a nearby genital site. In contrast, intra-anal warts are seen predominantly in patients who have had receptive anal intercourse. In women, external genital warts are more common than vaginal and cervical warts.

Symptoms Associated with Anogenital Warts

Most often genital warts cause minimal symptoms except for cosmetic concerns. Vulvar warts may cause dyspareunia, pruritus, and burning discomfort. Vaginal warts are usually asymptomatic, although occasional discharge, bleeding, or obstruction of the birth canal (due to increased wart growth during pregnancy) may occur. Penile warts may cause itching. Persons with urethral meatal warts may experience hematuria or impairment of the urinary stream. Perianal and intra-anal warts are usually asymptomatic but may cause pain, bleeding on defecation, or itching (Table 2).

Anogenital Warts in Preadolescent Children

Anogenital warts in preadolescent children may be due to sexual abuse, although this condition is not diagnostic for sexual abuse. Their appearance should prompt an evaluation by a clinician with special attention to other STIs and social risk factors. Anogenital warts in children may result from vertical
transmission, transmission of non-genital HPV types to the genital surface, and possibly fomite transmission, although fomite transmission has not been documented.

**Cervical Dysplasia**

Cervical dysplasia may be apparent on physical examination with visual inspection of the cervix, but typically the visualization of lesions requires additional modalities. The presence of anogenital warts provides evidence of HPV infection, but this does not consistently correlate with concomitant high-risk HPV infection or cervical dysplasia. Cervical cellular abnormalities are usually subclinical and lesions associated with these abnormalities can be detected by Papanicolaou smear test (Pap test) or colposcopy, with or without biopsy of the lesion. The application of 3% to 5% acetic acid (vinegar) and/or Lugol’s iodine to lesions has been used as a bedside screening tool, but is not routinely recommended. Magnification by colposcopy can enhance detection of cervical dysplasia; histology from a biopsy is used to confirm and stage cervical intraepithelial neoplasia (CIN). Low-grade cervical cellular abnormalities often regress spontaneously without treatment. Even high-grade CIN may regress without treatment, particularly for younger women (aged 21-24 years) so treatment recommendations vary according to age at CIN diagnosis.[39]

**Anal Dysplasia and Anal Cancer**

Anal dysplasia consists of pre-malignant cellular changes similar in nature to those seen in cervical dysplasia. The diagnosis is made based on biopsy of anal tissue, typically after high-resolution anoscopy. Patients with anal dysplasia most commonly have no symptoms and frequently have a normal physical examination (via standard anoscopy and digital anorectal examination). Some patients do describe anal pain, bleeding, or pruritus.[40] In some cases, physical examination may reveal anal lesions with a wide variety of appearances. Although certain physical examination findings, such as large or fixed lesions, ulceration, or bleeding, are more concerning for anal cancer, it is important to note that such findings do not establish a definitive diagnosis of malignancy, nor does the lack of symptoms or abnormal findings exclude the possibility of cancer. The roles of biopsy and high-resolution anoscopy are still being evaluated for both screening and diagnosis of anal dysplasia and cancer.

**Anogenital Cancers**

With progression from precancerous lesions to malignancy, the cervix or anal epithelium may become abnormal upon physical examination, with gross erosion, bleeding, ulcer, or mass. These abnormalities can extend from the cervix to vaginal mucosa or reveal tumor erosion into nearby tissue. Bimanual pelvic examination findings may disclose local metastatic involvement. Anorectal examination (via digital anorectal examination and anoscopy) may reveal an external or internal mass, with or without gross blood from tumor erosion. More than 90% of cervical and anal cancers are caused by HPV and HPV infection is linked to about 70% of vulvar, vaginal, and oropharyngeal cancers (Figure 9).[4,41]
Diagnosis

Anogenital Warts

Although most cases of anogenital warts are diagnosed clinically, confirmation by biopsy may be needed in the following situations:

- The diagnosis is uncertain.
- The patient is immunocompromised.
- Warts are pigmented, indurated, or fixed.
- The lesions do not respond to or worsen with standard treatment.
- There is persistent ulceration or bleeding.

Application of acetic acid is not routinely recommended due to its low specificity (many false-positives). External genital warts are not an indication for cervical colposcopy or type-specific HPV DNA testing. The CDC recommends screening persons with newly diagnosed anogenital warts for other STIs, including chlamydia, gonorrhea, HIV, and syphilis.

Cervical Cellular Abnormalities

Cytology

The Papanicolaou test, commonly referred to as a Pap smear, is a useful screening test to detect cervical cytologic abnormalities. The Papanicolaou test is named after Georgios Papanikolaou, the physician who determined the test could be used to screen for cervical abnormalities and cervical cancer. Although the Pap smear is not a test for HPV per se, it provides indirect evidence of HPV infection because it detects epithelial cellular changes that are almost always due to HPV. The results of the cytologic evaluation are classified by a pathologist (according to the 2014 Bethesda System) to guide subsequent work-up or treatment.[42] Notably, the frequency of Pap test screening remains the same regardless of HPV vaccination status or history of external genital warts (assuming the patient is receiving screening at intervals recommended by her health care provider).

High-Risk HPV Nucleic Acid Testing

A definitive diagnosis of HPV infection is based on detection of viral nucleic acid (DNA or mRNA). Clinical HPV tests that detect different high-risk types of HPV DNA in cells scraped from the cervix are commercially available. These tests evaluate a wide range of high-risk HPV types and have been approved by the United States Food and Drug Administration for: (1) triage of women with atypical squamous cells of undetermined significance (ASCUS) Pap test findings aged 21 years and older, and (2) screening of women aged 30 years and older in conjunction with the Pap test. Use of HPV DNA testing for women with low- or high-grade squamous intraepithelial lesion (LSIL or HSIL) Pap test findings is unnecessary because the vast majority of women with these findings are infected with HPV. Use of type-specific HPV tests for routine diagnosis and management of genital warts is not recommended. Use of HPV tests in women 20 years and younger is not routinely recommended as it has little clinical utility.[43] HPV tests are not FDA-approved for use in men, nor are they approved for general STD testing. In the following situations, HPV testing (including oncogenic HPV and HPV 16/18 tests) is NOT indicated:

- Deciding whether to vaccinate against HPV
- Conducting STD screening in women or men at risk for STDs
- Providing care to persons with genital warts or their partners
- Conducting screening for cervical cancer as a stand-alone test (i.e., without a concurrent Pap test)
- Testing women younger than age 30 years of age as part of routine cervical cancer screening
• Testing oral or anal specimens.

**Reporting and Public Health Follow-Up**

HPV infection is not reportable in any state. Some states have made cervical precancer reportable. Check with your local health department for reporting requirements for HPV-associated outcomes in your area.
Screening for HPV Infection and Dysplasia

Since many HPV infections are clinically silent or self-resolving, routine screening for HPV infection is not recommended by the CDC or the United States Preventive Services Task Force (USPSTF). Screening is targeted at cervical cellular abnormalities caused by HPV infection in order to focus on those patients at highest risk for progression to malignancy. Anal screening for precancer is not currently recommended by the CDC. [44]

Screening for HPV-associated Cancers and Precancers

There is ample evidence for the effectiveness of screening for HPV-associated precancer in women. Recommendations for screening algorithms are very similar across major medical organizations including the American Cancer Society (ACS),[45], American College of Obstetricians and Gynecologists (ACOG), and USPSTF.[46] We would like to point out these guidelines do not fully address cervical cancer screening in transgender individuals. It is important to note that when using the guidelines below, cervical cancer screening should be based on whether the individual has a cervix, not on the identified gender of the individual. For example, a transgender man (female-to-male) who identifies as a man, has a cervix and needs cervical cancer screening. In contrast, a transgender woman (male-to-female) who identifies as a woman, does not have a cervix and does not need cervical cancer screening. Similarly, for gender-fluid individuals, cervical cancer should solely be based on whether they have a cervix.

- Routine cervical screening should be performed starting at age 21 years and continue through age 65 years to prevent invasive cervical cancer. Testing can be performed using either conventional or liquid-based cytologic tests (i.e., Pap tests).
- For women aged 30 years or older, screening can include one of several FDA-approved oncogenic or high-risk HPV (hr-HPV) tests.
- Annual cervical cancer screening is no longer recommended for all women. Instead, Pap testing is recommended every 3 years from ages 21–29 years. From ages 30–65 years, women should either receive a Pap test every 3 years or a Pap test plus HPV test (co-test) every 5 years. Because of the high negative predictive value of two tests, women in this age group who test negative for both HPV and Pap do not requiring screening again for 5 years.
- Cervical screening programs should screen women who have received HPV vaccination in the same manner as unvaccinated women.
- Although the prevalence of oncogenic HPV types are high in females younger than 21 years of age, the oncogenic HPV and squamous intraepithelial lesions caused by HPV in adolescent girls are more likely to regress in these younger women than in older women. Thus, Pap testing is not recommended before age 21 years of age.

The CDC 2015 STD Treatment Guidelines[44] additionally recommend the following practices:

- The Pap test should not be considered a screening test for STDs.
- All women should receive cervical cancer screening, regardless of sexual orientation (i.e., women who identify as lesbian, bisexual, or heterosexual) or gender identity.
- Liquid-based cytology is an acceptable alternative to conventional Pap tests, as it has similar test-performance characteristics.
- Ideally, women should be advised to have a Pap test 10 to 20 days after the first day of menses. However, this test can be performed during menstruation depending on menstrual flow and type of cytology used (liquid-based cytology can differentiate cells from blood and mucus; conventional Pap test might not).
- If specific sexually transmitted infections other than HPV (e.g., chlamydia or gonorrhea) are identified at the visit, the woman might need to have a repeat Pap test after appropriate treatment for those infections. In most instances (even in the presence of some severe infections), Pap tests will be reported as satisfactory for evaluation, and reliable final reports can be produced without the need to repeat the Pap test after treatment is received.
• The presence of a mucopurulent discharge should not postpone Pap testing. The test can be performed after removal of the discharge with a saline-soaked cotton swab.
• In the presence of cervical friability, liquid-based cytology should be used; conventional Pap testing might need to be deferred in the presence of heavy bleeding until cervicitis is treated.
• The presence of external genital warts is not an indication to have more frequent Pap testing.
• The sequence of Pap testing in relation to collection of other endocervical specimens does not influence Pap test results or their interpretation. In general, vaginal specimens are preferred for chlamydia and gonorrhea screening in women, but in the setting of a pelvic exam, endocervical specimens for STD testing can be collected first.
• Women who have had a total hysterectomy do not require a routine Pap test unless the hysterectomy was performed because of cervical cancer or its precursor lesions. In women whose cervix remains intact after a hysterectomy, regularly scheduled Pap tests should be performed as indicated.
• Health care facilities that train providers on Pap test collection and employ simple quality assurance measures are more likely to obtain satisfactory test results (as determined by the laboratory).
• Use of instruments designed to obtain sample from the cervical transformation zone (e.g., cytobrushes) improves the accuracy of Pap tests.
• At an initial visit, medical providers should ask women about their most recent Pap test and results and history of evaluation and treatment (e.g., loop electrosurgical excision procedure and colposcopy) to assist with management; every effort should be made to obtain copies of recent results. The importance and frequency of Pap testing or co-testing (Pap and HPV testing) should be reinforced.

Screening for Cervical Cancer in Women who are Pregnant

Screening for cervical cancer in pregnant women should be screened at the same intervals as nonpregnant women. In this setting, a swab, Ayre’s spatula, or cytobrush can be used for obtaining Pap tests in pregnant women. Abnormal results should be referred to a specialist for discussion of treatment options.

Screening for Cervical Cancer in Women with HIV Infection

Several studies have documented an increased risk for cervical precancers and cancers in women with HIV infection. Per Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, all women newly diagnosed with HIV infection should receive baseline cervical cancer screening within 1 year of the onset of sexual activity (regardless of the mode of HIV transmission) and no later than 21 years of age.

• **Women Younger than 30 Years of Age:** If the initial Pap test is normal, then follow-up Pap testing should be performed every 12 months; some experts also recommend a Pap test at 6 months after the baseline test. If the results of 3 consecutive Pap tests are normal, the interval for follow up Pap testing should extend to every 3 years. For women younger than 30 years of age, co-testing (Pap test and HPV test) is not recommended.

• **Women 30 Years of Age and Older:** In contrast to recommendations for the general population, cervical cancer screening in women with HIV infection should continue throughout the woman’s lifetime and not end at 65 years of age. For women 30 years of age and older, the acceptable screening method is either Pap testing alone or co-testing with Pap and HPV. If screening with Pap tests alone, the Pap test should be performed at the time of HIV diagnosis (baseline), then every 12 months; some experts also recommend a Pap test at 6 months after the baseline test. If the results of 3 consecutive Pap tests are normal, follow-up Pap tests should be every 3 years. If co-testing with Pap and HPV test is available, then co-testing can be done at the time of diagnosis. Women that have negative co-testing (a normal Pap and negative HPV test) can have their next screening for cervical cancer performed in 3 years. Women with a normal Pap test but a positive HPV test should have co-testing repeated in 1 year; for the repeat co-testing in 1 year, if either test is positive (abnormal Pap or positive HPV test), then the woman should be referred for colposcopy. Similarly, if genotype testing is performed and is positive for HPV16 or 16/18, then referral for colposcopy is recommended.
Management of Cervical Cellular Abnormalities

Management of cervical cellular abnormalities is complex and requires synthesis of patient age, Pap test results, biopsy pathology, and high-risk HPV DNA testing. High-risk HPV DNA co-testing serves primarily to allow safe deferment of lower risk lesions and cellular abnormalities of undetermined significance. The approach and management of patients with cervical cellular abnormalities is beyond the scope of this module, but is addressed in the 2012 American Society for Colposcopy and Cervical Pathology (AASCP) Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors.[39] The 2015 CDC STD Treatment Guidelines summarize key points from the AASCP consensus guidelines.[39,44]

- Women aged 21–24 years are managed more conservatively than other women because of potential harms of over treatment and low risk for cancer. For women in this group with ASCUS or LSIL, repeat cytology in 12 months.
- For women with ASCUS cytology, either cytology can be repeated in 12 months (for women of all ages) or reflex HPV testing can be performed (for women aged 25 years and older).
- For women with ASCUS who are HPV negative, a repeat HPV and Pap test in 3 years is recommended.
- For women who have normal cytology but lack endocervical cells, a repeat Pap is not required.
- For women who have unsatisfactory cytology, regardless of negative HPV result, a repeat cytology is required in 2–4 months.
- HPV 16/18 testing is acceptable for women who have discordant results (normal Pap test accompanied by a positive HPV test). If the HPV 16/18 test is positive, women should immediately receive colposcopy. If negative, these women should repeat the HPV co-test in 1 year.
- For women with LSIL or HSIL, the management should be provided by a specialist and according to existing guidelines.

Screening for Anal Cancer

Data are insufficient to recommend routine anal cancer screening with anal cytology in MSM (without HIV infection), heterosexual men and women, and in persons with HIV infection. Evidence is limited on natural history of anal intraepithelial neoplasia, reliability of screening methods, safety and response to treatments, and programmatic considerations. An annual digital anorectal examination may be useful to detect masses on palpation that could be anal cancer in persons with HIV infection and possibly HIV-negative MSM with a history of receptive anal intercourse.[44] Some clinical centers perform anal cytology to screen for anal cancer among high-risk populations (e.g., persons with HIV infection and MSM), followed by high-resolution anoscopy (HRA) for those with abnormal cytologic results. Initiating anal Pap testing in MSM should only be done if the center has developed a system to manage and follow those individuals with initial abnormal anal Pap smears. Oncogenic HPV tests are not clinically useful for anal cancer screening among MSM because of a high prevalence of anal HPV infection.
Treatment

Anogenital Warts

Goals of Wart Treatment

The primary goal of treatment is the removal of visible warts.[49] If left untreated, visible genital warts persist with or without proliferation, but some regress spontaneously. Currently available therapies may reduce infectivity, but probably not completely. There is no evidence that presence of genital warts is associated with development of cervical or anal cancer, and there are no data that suggest treatment of genital warts impacts the subsequent risk of anogenital HPV-related cancer. Treatment of warts should be guided by several factors, including preference of the patient, available resources, experience of the health care provider, location of the lesion(s), and pregnancy status. Most patients have fewer than ten genital warts and most have a total wart area less than 1.0 cm$^2$. The warts with a relatively small area respond to a wide range of treatment modalities. In most patients, appropriate treatment can induce wart-free periods. Among the treatments recommended in the CDC STD Treatment Guidelines, there is no evidence that any one treatment is superior to others, and no specific treatment is ideal for all patients or for all warts.

Selection of Therapy for Anogenital Warts

Although the CDC treatment guidelines do not provide an algorithm to guide selection of treatment modality for genital warts, the use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes. The major decision points for a provider and patient are whether or not to treat, and, if treating, whether to utilize patient- or provider-applied therapy. Because of uncertain benefit of wart treatment on future HPV transmission and the possibility for spontaneous resolution, some patients may choose to forgo treatment and await possible spontaneous resolution. Even with successful treatment, subsequent recurrences are common, with a 20 to 50% recurrence rate at 3 to 6 months post-treatment.[50] Selection of specific therapies is based on lesion location, provider experience, availability, and patient preference.[49] Cryotherapy and surgical removal are feasible options in all anatomic locations. Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) is acceptable in vaginal, cervical, and intra-anal warts. The use of TCA, BCA, or podophyllin is contraindicated for urethral meatus warts.

Recommended Therapy for External Anogenital Warts

Multiple patient-applied and medical provider-administered therapies are recommended as options for the treatment of external anogenital warts (Table 3).[49] Although provider-administered therapies often result in more rapid resolution and require fewer treatments than patient-applied modalities, many patients prefer to self-administer therapy for their warts due to convenience and the ability to administer the treatment in the privacy of their home. Medical providers should have appropriate knowledge and training for at least one provider-administered and one patient-applied treatment. Many patients require multiple courses of therapy rather than a single treatment. Complications rarely occur if treatments for warts are properly employed. Reappearance of genital warts within the first several months after treatment is common and usually indicates recurrence rather than reinfection.

Alternative Therapy for External Anogenital Warts

Limited data are available regarding the efficacy of alternative regimens for treating external anogenital warts, but successful treatment has been reported with podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir.[49] Podophyllin resin is has been associated with multiple reports of systemic toxicity when this agent was applied to large lesions or when left on for longer periods than recommended.[51] Podophyllin resin might be considered as an alternative under strict adherence to recommended practice, but routine use of this topical agent is not recommended.
Therapy for Internal Anogenital Warts

The management of internal anogenital warts, including warts located in the urethral meatus, vagina, cervix, or and intra-anal region, are complicated to treat, and, in many instances may require management or consultation with a specialist (Table 4).

Genital Wart Follow-Up

The presence of genital warts is NOT an indication for increase in frequency of Pap test screening (assuming the patient with genital warts is receiving screening at intervals recommended by a health care provider) or for cervical colposcopy. While follow-up evaluation is not mandatory, it provides an opportunity to monitor for complications of therapy, document absence of warts, and reinforce patient education and counseling messages. Patients concerned about recurrences should be offered a follow-up evaluation three months after treatment.

Special Management Considerations

Genital Warts during Pregnancy

Genital warts can proliferate rapidly and become more friable during pregnancy. Watchful waiting is acceptable with smaller lesions. During pregnancy, cryotherapy, trichloroacetic acid, bichloroacetic acid, and surgical removal may be used. Cytotoxic agents (podophyllin, podofilox, imiquimod) should not be used. Although pregnant women with genital warts have a risk of transmitting HPV to their child during a vaginal birth, Cesarean section delivery should not be performed solely to prevent transmission to the neonate.

Management of Genital Warts in Immunocompromised Patients

The general approach to the treatment of genital warts in persons with HIV infection is the same as for those without HIV infection.[49] Persons living with HIV infection, particularly those individuals with advanced immunosuppression, often have larger or more numerous warts that do not respond as well to therapy and recurrences occur more frequently after treatment. High-grade squamous intraepithelial lesions (HSIL) and invasive cancer arising within the region of a genital wart (or resembling genital warts) are more frequent in immunocompromised patients; therefore, hyperpigmented lesions and lesions that persist despite treatment (especially in the perianal area) should be promptly evaluated by biopsy. The role of genital warts (or irritated post-treatment sites) in HIV transmission has not been well characterized.
Prevention

Behavioral Prevention Measures

Abstaining from sexual activity remains the most reliable method for preventing genital HPV infection. Patients can decrease their chances of infection by practicing consistent and correct condom use and by limiting their number of sex partners. Although these interventions might not fully protect against HPV, they can decrease the chances of HPV acquisition and transmission.

HPV Vaccines

The HPV vaccine is based on recombinant technology that produces L1 major protein, which self-assemble into viral-like particles (Figure 10).[23] The CDC has suggested that full vaccination coverage could prevent future HPV-attributable cancers and potentially reduce racial and ethnic disparities in HPV-associated cancer incidence in the United States.[10] The introduction and use of safe and effective vaccines against common HPV types is having a significant impact on the morbidity and mortality associated with HPV infection among vaccinated populations.[15,52,53,54]

FDA Approved HPV Vaccines

Three HPV vaccines have been licensed in the United States: a bivalent vaccine (2vHPV) that prevents infection with HPV types 16 and 18, a quadrivalent vaccine (4vHPV) that prevents infection with HPV types 6, 11, 16, and 18, and a 9-valent vaccine (9vHPV) that prevents infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.[13,55] In the United States, the 9vHPV is now the only available HPV vaccine and it offers protection against 7 oncogenic HPV types (16, 18, 31, 33, 45, 52, and 58), which account for approximately 80% of cervical cancers, and 2 HPV types (6 and 11) that cause approximately 90% of genital warts.[13] The HPV vaccines have shown excellent safety and efficacy in females and males.[55,56,57,58,59]

Indications for 9vHPV Vaccine

The current FDA indications for the 9vHPV vaccine for females and males are outlined below. The 9vHPV vaccine was FDA-approved in 2014 for males and females 9 through 26 years of age.[13] The age indication for 9vHPV vaccine was recently expanded by the FDA to include women and men 27 though 45 years of age.[60] This change was based on unpublished data from a study that evaluated the effectiveness and safety of 9vHPV vaccine in approximately 1,200 women 27 through 45 years of age; the women were followed for an average of 3.5 years after immunization and 9vHPV was 88% effective in preventing combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine.[60] Although the study only included women, the age approval was also extended for men based on data in younger men and immunogenicity data in a study of 150 men 27 through 45 years of age.[56,60,61]

- **Females:** The 9vHPV is approved for females aged 9 through 45 years of age for prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58; precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV types 6 and 11.
- **Males:** The 9vHPV is approved for males aged 9 through 45 years of age for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58; precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV types 6 and 11.

Dosing and Schedule for 9vHPV Vaccine

The FDA recommended dosing schedule depends on the age of the individual receiving the vaccine series.
Persons Aged 9 through 14 Years: Healthy girls and boys in this age range have the option to receive a 2-dose series given at 0 and 6-12 months or 3-dose series given at 0, 2 months, and 6 months. Note that with the 2-dose series, if the person received the second vaccine dose earlier than 5 months after the first dose, then a third dose should be administered at least 4 months after the second dose.

Persons Aged 15 through 45 Years: All persons in this age range should receive the 3-dose vaccine series given at 0, 2 months, and 6 months.

Advisory Committee for Immunization Practices (ACIP) 9vHPV Recommendations

The following summarizes key ACIP recommendations for the use of the 9vHPV vaccine.

- **Age of Immunization and Age Range:** The ACIP recommends routine administration of 9vHPV at age 11 or 12 years for both girls and boys; the vaccine can be given as early as age 9 years for children who have experienced sexual abuse or sexual assault. The ACIP recommends 9vHPV can be given through age 26 years for females and males. The ACIP recommends that persons 27 through 45 years of age who have not previously received HPV vaccine engage in shared decision making with their clinician regarding vaccination with 9vHPV, as the public health benefit of 9vHPV in older individuals is not clear since many individuals in this age range have already been infected with multiple HPV types.

- **Dosing Schedule:** The ACIP recommend use of a 2-dose HPV vaccine schedule for healthy girls and boys who initiate the vaccination series at ages 9 through 14 years; the 2nd dose should be given 6 to 12 months after the initial dose. Teens and young adults who start the series after 15 years of age require three doses of HPV vaccine to ensure adequate protection; this consists of a 3-dose series of IM injections over a 6-month period, with the second and third doses given 1-2 months and 6 months after the first dose, respectively.

- **Recommended Minimal Intervals Between Doses:** For the 2-dose vaccine series, the ACIP recommends a minimum interval of 5 months; if the second dose is administered prior to an interval of 5 months, then a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of 5 months after the first dose. For the 3-dose series, the ACIP recommends a minimal of 4 weeks between the first and second doses, 12 weeks between the second and third doses, and 5 months between the first and third doses; if any dose of the vaccine is administered prior to the recommended minimal interval, it should be readministered after another minimum interval has elapsed since the most recent dose.

- **Persons with Primary or Secondary Immunocompromising Conditions:** The three dose vaccine series should be used for all persons with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, including HIV infection, malignant neoplasms, autoimmune disease, or immunosuppressive therapy, transplantation, B lymphocyte antibody deficiencies, and T lymphocyte complete or partial defects.

- **Interrupted Schedule:** If the vaccine schedule is interrupted for longer than the recommended dosing interval, the recommendation is to complete the series without repeating any of the doses. Note that the total number of vaccine doses is based on the age when the first dose was given.

- **Persons who Previously Received an HPV Vaccine other than 9vHPV:** Persons who previously received 2 doses of either 2vHPV or 4vHPV and the series was initiated prior to age 15 are considered adequately vaccinated. For persons who received an incomplete vaccine series with 2vHPV or 4vHPV, the 9vHPV vaccine can be used to complete the series. The ACIP does not provide a recommendation for or against giving 9vHPV to persons who previously received a recommended vaccine series with 2vHPV or 4vHPV.

Financial Assistance for HPV Vaccine

Funding for the HPV vaccine is available for eligible children and adolescents aged younger than 19 years of age through the Vaccines for Children (VFC) program; information regarding this program is available by...
Population Impact of HPV Vaccine

In the United States, a significant decline in vaccine-targeted HPV strains occurred following widespread HPV immunization. Within 6 years of HPV vaccine introduction, the prevalence of the four vaccine-targeted HPV types among decreased 64% among females 14 through 19 years of age and 34% among females 20 through 24 years of age.\[11,12\] Additional studies in the United States, Australia, and Canada, have shown a similar impact with HPV vaccine.\[7,15,64\] Several studies have also documented declines in vaccine-targeted types among non-immunized women, suggesting early development of “herd immunity.” Based on HPV typing data from samples taken from patients associated cancers of the vulva, vagina, anus, penis, and oropharynx, the HPV 9-valent vaccine (9vHPV) will substantially reduce most HPV-related cancers (Figure 11).\[4\] In Australia, an aggressive and highly successful HPV vaccine initiative has resulted in the marked reduction in HPV-related disease, with the hope of future elimination of vaccine-type HPV disease in Australia.\[65,66\] Taken together, these studies highlight a robust, protective effect from HPV vaccine and highlight the importance of efforts to maximize vaccine uptake.

Cervical Cancer Screening

The cervical Pap test is an effective, low-cost screening test for preventing invasive cervical cancer, an HPV-associated disease. Although this practice does not prevent primary HPV infection, it has a significant effect on morbidity and mortality associated with cervical cancer.
Patient Counseling and Education

Patient counseling and education should cover the nature of HPV infection, transmission issues, and risk reduction. Most women infected with HPV will clear the infection within 2 years.

Nature of HPV Infection

Patients should be informed that:

- Genital HPV is a very common viral infection in sexually active adults.
- Low-risk genital HPV types are associated with mild Pap test abnormalities and genital warts. High-risk types are associated with mild to severe Pap test abnormalities and, rarely, cancers of the cervix, vulva, vagina, anus, penis, and oropharynx.
- Although infection is usually self-limited, recurrence of genital warts within the first several months after treatment is common.

Transmission

The following transmission-related issues should be discussed with patients:

- Genital HPV infection is usually sexually transmitted.
- The incubation period is variable, and determining the timing and source of infection is frequently difficult.
- Recurrences of genital warts usually do not represent reinfection.
- Once infected, transmission risk to current and future partners is unclear.
- Although less likely, it is possible to transmit to partners despite lack of visible lesions.
- Consistent and correct condom use has been associated with lower rates of genital warts and cervical cancer, but HPV infections can occur in male and female genital areas that are not covered or protected by a condom.
- The duration of infectivity after wart treatment is unknown.
- The value of disclosing a past diagnosis of genital HPV infection to future partners is unclear, although candid discussions about past STDs should be encouraged and attempted whenever possible.

Risk Reduction

The clinician should:

- Assess the patient's behavior-change potential.
- Develop individualized risk-reduction plans with the patient for lasting results.
- Discuss prevention strategies such as abstinence, condoms, and limiting the number of sex partners, etc.

Partner Management

Sex partner evaluation is not necessary for management of genital warts because there are no data to indicate that reinfection plays a significant role in recurrences. Providing treatment solely for the purpose of preventing future transmission cannot be recommended because the value of treatment in reducing infectivity is not known. Sex partner counseling provides an opportunity for these partners to learn about the implications of having a partner who has genital warts and about their own potential for future disease transmission. Genital warts are highly infectious, so it benefits the partner to be informed and for the couple to use risk-reduction methods such as consistent and correct condom use to reduce the risk of transmission. Partner counseling also provides an opportunity to offer these partners STD and Pap screening (if appropriate), and counseling on prevention.
Counsel patients to:

- Watch for clinical recurrences (most frequently occurring in first three months after treatment).
- Continue regular Pap screening at the same intervals as recommended for women WITHOUT genital warts.
- Communicate to current sex partners about a current diagnosis of genital warts and the risk for transmission. Patients should have no sexual activity with new partners until warts are gone or removed.
- Sex partners of persons with genital warts should receive the 9vHPV vaccine if they have not previously received an HPV vaccine (and they are eligible to receive HPV vaccine).
- Patients can still potentially transmit HPV to sexual partners after visible warts are gone since HPV can remain persistent in the tissues.
- The risk of transmitting HPV to sexual partners is likely lowered by consistent and correct use of condoms, but transmission can potentially still occur via contact with areas of skin that cannot be covered with a condom.

**Educational Resources**

The following resources are available for HPV-related patient educational materials:

American Congress on Obstetrics and Gynecology (ACOG)-Cervical Cancer Screening

CDC Cervical Cancer Screening Fact Sheet

CDC Division of STD Prevention—Human Papillomavirus

National Cancer Institute: Cervical Cancer Screening—Patient Version

National HPV and Cervical Cancer Prevention Resource Center
Summary Points

- Human papillomavirus (HPV) is one of the most common sexually transmitted infections with more than 100 subtypes, which are divided into low-risk (non-oncogenic) types and high-risk types (oncogenic types).
- Low-risk HPV types 6 and 11 cause approximately 90% of genital warts; high-risk HPV types 16 and 18 account for approximately 63% of all HPV-associated cancers and about 70% of cervical cancers, and high-risk HPV types 31, 33, 45, 52, and 58 account for an additional 10% of cervical cancers.
- Most HPV infections, whether caused by low-risk or high-risk types, are transient (resolve within 2 years), asymptomatic, and have no clinical consequences.
- Genital warts caused by HPV have four morphologic types: condylomata acuminata, smooth papules, flat papules, and keratotic warts.
- There is strong evidence to support screening for HPV-associated pre-malignancy lesions in women aged 21 to 65 years with cervical Pap testing (and HPV screening in women 30 years of age or older), and several algorithms have been published to guide screening and the management of abnormal results.
- Women with HIV infection have an increased risk of cervical precancers and cancers and require more frequent Pap screening.
- Data are insufficient to recommend routine anal cancer screening, though some centers screen high-risk populations (men who have sex with men, persons with HIV infection, persons with a history of receptive anal intercourse) with anal cytology.
- Consistent and correct use of condoms reduces the risk for genital HPV acquisition or transmission but does not entirely prevent transmission of HPV.
- The availability of effective HPV vaccines has led to a decline in some but not all sequelae of HPV infections among women in the United States.
- There are three HPV vaccines that have been licensed in the United States. The 9-valent HPV vaccine (9vHPV) is the major HPV vaccine used and this vaccine prevents infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.
Citations


60. U.S. Food and Drug Administration: FDA News Release. FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. October 5, 2018. [U.S. Food and Drug Administration]


[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

References

  [PubMed Abstract]

  [PubMed Abstract]

  [PubMed Abstract]

  [PubMed Abstract]

  [PubMed Abstract]

  [PubMed Abstract]

  [PubMed Abstract]

  [PubMed Abstract]


Centers for Disease Control and Prevention (CDC). Human Papillomavirus (HPV) Vaccine Safety. [CDC] -

• Centers for Disease Control and Prevention (CDC). Supplemental information and guidance for vaccination providers regarding use of 9-valent HPV. November 29, 2016
[CDC] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -


Friedman AL, Shepheard H. Exploring the knowledge, attitudes, beliefs, and communication preferences of the general public regarding HPV: findings from CDC focus group research and implications for practice. Health Educ Behav. 2007;34:471-85.


[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]


Kumar B, Narang T. Local and systemic adverse effects to topical imiquimod due to systemic immune stimulation. Sex Transm Infect. 2011;87:432. [PubMed Abstract] -


Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent Human
[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -


• Schim van der Loeff MF, Mooij SH, Richel O, de Vries HJ, Prins JM. HPV and anal cancer in HIV-infected


  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

  [PubMed Abstract] -

• The National Institute for Occupational Safety and Health (NIOSH). Control of smoke from laser/electrical surgical procedures. DHHS (NIOSH) Publication Number 96–128.
  [CDC] -

  [PubMed Abstract] -

  [PubMed Abstract] -


Figures

Figure 1 Anogenital Warts—Initial Visits to Physicians’ Offices, United States, 1966-2014

Figure 2 Cervicovaginal Prevalence of Human Papillomavirus Types 6, 11, 16 and 18

This graph shows the cervicovaginal prevalence of human papillomavirus types 6, 11, 16 and 18 among women aged 14–34, with the prevalence broken out by age group and time period. The data was collected from the NHANES Surveys in 2003–2006 and 2009–2012.

**Figure 3 Anogenital Wart Prevalence—United States, 2003-2010**

This graphic shows the annual anogenital wart prevalence (per 1000 person-years) in the United States for male and female private insurance enrollees aged 10-39 years of age. These data are from Truven Health Analytics MarketScan Commercial Claims and Encounters Database, United States, 2003–2010.

Figure 4 Human Papillomavirus Type 16

Human papillomavirus is a small, non-enveloped, double-stranded DNA virus that is approximately 55 nm in diameter. The virus has an icosahedral shell primarily consisting of 360 molecules of the L1 major capsid protein arranged as surface 72 pentamers (light blue). The outer shell also contains the L1 minor protein. This illustration shows the structure for human papillomavirus type 16.

Figure 5 Human Papillomavirus Type 16 Major Capsid Protein L1

The human papillomavirus type major protein L1 is a pentameric capsomere that forms the exterior surface of a virion. This illustration shows a single major capsid protein L1 from human papillomavirus type 16. This protein has the capacity to self assemble to form the virus outer shell and this property is exploited in the human papillomavirus vaccine technology.

**Figure 6 Age at Peak Prevalence for Each Stage in Cervical Carcinogenesis**

Natural history of HPV infection and cancer as shown at top. The bottom graph shows the correlation of the stages during the natural history with age. As shown in the graph, the age of peak high-grade intraepithelial lesion (HSIL) or precancer occurs 5 to 10 years after HPV infection.

**Figure 7 Perineal Warts**

Extensive warts at the base of the scrotum and perianal region.

Source: photograph from Public Health—Seattle & King County STD Clinic
Figure 8 Warts on Cervix

Source: photograph by Claire Stevens, PA Public Health—Seattle & King County STD Clinic
**Figure 9 Human Papillomavirus Detection at Cancer Site**

These data are from archival tissue for cancers diagnosed from 1993 to 2005 obtained by the CDC in partnership with seven US population-based cancer registries. The investigators performed HPV testing on samples from 2670 patients.

**Figure 10 Human Papillomavirus Vaccine Production**

Conceptual rendition of production of human papillomavirus vaccine. The vaccine process involves recombinant synthesis of major capsid L1 proteins that self-assemble as a shell of 72 pentameric capsomeres to form viral-like particles (VLPs). The assembled pseudovirus is very similar to the native human papillomavirus and is highly immunogenic.

Illustration by David H. Spach, MD
Figure 11 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine

Image 11A: HPV Types and Cervical Cancer

Figure 11 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine
Image 11B: HPV Types and In Situ Cervical Cancer

Figure 11 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine
Image 11C: HVP Types and Vulvar and Cancer

Figure 11 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine
Image 11E: HPV Types and Vaginal and Cancer

Figure 11 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine

Image 11F: HPV Types and Anal Cancer

Figure 11 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine

Image 11G: HPV Types and Penile Cancer

Table 1.

**Human Papillomavirus Types**

<table>
<thead>
<tr>
<th>Low-Risk Types (non-oncogenic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Associated with genital warts and benign or low-grade cervical cellular changes (mild Pap test abnormalities).</td>
</tr>
<tr>
<td>• Approximately 90% of genital warts are caused by HPV types 6 and 11.</td>
</tr>
<tr>
<td>• The HPV types causing genital warts can occasionally cause lesions on oral, upper respiratory, upper gastrointestinal, and ocular locations. Recurrent respiratory papillomatosis, a rare condition, is usually associated with HPV types 6 and 11.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-Risk Types (oncogenic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Associated with low-grade cervical cellular changes, high-grade cervical cellular changes (mild, moderate, and severe Pap test abnormalities), and cervical dysplasia. In rare cases, associated with anogenital (i.e., cervical, vulvar, vaginal, anal, penile, and oropharyngeal) cancers.</td>
</tr>
<tr>
<td>• HPV types 16 and 18 account for approximately 63% of all HPV-associated cancers and about 66% of cervical cancers.</td>
</tr>
<tr>
<td>• The HPV types 31, 33, 45, 52, and 58 cause approximately 10% of all HPV-associated cancers.</td>
</tr>
<tr>
<td>Differential Diagnoses for Anogenital Warts</td>
</tr>
<tr>
<td>--------------------------------------------</td>
</tr>
<tr>
<td><strong>Manifestations of Other Genital Infections</strong></td>
</tr>
<tr>
<td>• Condylomata lata (manifestation of secondary syphilis)</td>
</tr>
<tr>
<td>• Molluscum contagiosum</td>
</tr>
<tr>
<td><strong>Acquired Dermatologic Conditions</strong></td>
</tr>
<tr>
<td>• Seborrheic keratosis</td>
</tr>
<tr>
<td>• Lichen planus</td>
</tr>
<tr>
<td>• Fibroepithelial polyp, adenoma</td>
</tr>
<tr>
<td>• Melanocytic nevus</td>
</tr>
<tr>
<td>• Neoplastic lesions</td>
</tr>
<tr>
<td><strong>Normal Anatomic Variants</strong></td>
</tr>
<tr>
<td>• &quot;Pink pearly penile papules&quot;</td>
</tr>
<tr>
<td>• Vestibular papillae (micropapillomatosis labialis)</td>
</tr>
<tr>
<td>• Skin tags (acrochordons)</td>
</tr>
<tr>
<td><strong>External Genital Squamous Intraepithelial Lesions (SIL)</strong></td>
</tr>
<tr>
<td>• Squamous cell carcinoma in situ</td>
</tr>
<tr>
<td>• Bowenoid papulosis</td>
</tr>
<tr>
<td>• Erythroplasia of Queyrat</td>
</tr>
<tr>
<td>• Bowen’s diseases of the genitalia</td>
</tr>
</tbody>
</table>
Table 3. 2015 STD Treatment Guidelines: Anogenital Warts
Treatment of External Anogenital Warts

External anogenital warts include penis, groin, scrotum, vulva, perineum, external anus, and perianus*

<table>
<thead>
<tr>
<th>Recommended for PATIENT-APPLIED Therapy</th>
<th>Podofilox 0.5% solution or gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply podofilox solution (using a cotton swab) or podofilox gel (using a finger) to anogenital warts twice a day for 3 days, followed by 4 days of no therapy. Repeat the cycle, as necessary, for up to four cycles.</td>
<td></td>
</tr>
</tbody>
</table>

The total wart area treated should not exceed 10 cm², and the total volume of podofilox should be limited to 0.5 mL per day.

<table>
<thead>
<tr>
<th>Recommended for PATIENT-APPLIED Therapy</th>
<th>Imiquimod 3.75% cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply the 3.75% cream once at bedtime, every night consecutively for 16 weeks. The treatment area should be washed with soap and water 6-10 hours after the application.</td>
<td></td>
</tr>
</tbody>
</table>

Note: Imiquimod might weaken condoms and vaginal diaphragms.

<table>
<thead>
<tr>
<th>Recommended for PATIENT-APPLIED Therapy</th>
<th>Imiquimod 5% cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply the 5% cream once at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6-10 hours after the application.</td>
<td></td>
</tr>
</tbody>
</table>

Note: Imiquimod might weaken condoms and vaginal diaphragms.

<table>
<thead>
<tr>
<th>Recommended for PATIENT-APPLIED Therapy</th>
<th>Sinecatechins 15% ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply three times daily (0.5 cm strand of ointment to each wart) using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved. This product should not be continued for longer than 16 weeks. Do not wash off after use.</td>
<td></td>
</tr>
</tbody>
</table>

Note: Sinecatechins might weaken condoms and vaginal diaphragms.

<table>
<thead>
<tr>
<th>Recommended for PROVIDER-ADMINISTERED Therapy</th>
<th>Cryotherapy with liquid nitrogen or cryoprobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large.</td>
<td></td>
</tr>
</tbody>
</table>

Health care providers must be trained on the proper use of this therapy because over- and under-treatment can result in complications or low efficacy.

<table>
<thead>
<tr>
<th>Recommended for PROVIDER-ADMINISTERED Therapy</th>
<th>Surgical removal either by tangential scissor excision, tangential shave</th>
</tr>
</thead>
<tbody>
<tr>
<td>After local anesthesia is applied, anogenital warts can be physically destroyed by electrocautery, in which case no additional hemostasis is required. Alternatively, the warts can be removed either by tangential excision with a pair of fine scissors or a scalpel, by carbon dioxide (CO2) laser, or by curettage.</td>
<td></td>
</tr>
</tbody>
</table>

Surgical therapy has the advantage of eliminating most warts at a single visit, although recurrence can occur. Surgical removal requires substantial clinical training, additional equipment, and sometimes a longer office visit.
Recommended for PROVIDER-ADMINISTERED Therapy

Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80-90% solution

A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid. TCA/BCA treatment can be repeated weekly if necessary.

TCA solution has a low viscosity comparable with that of water and can spread rapidly and damage adjacent tissues if applied excessively.

*Many persons with external anal warts also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy.

### Table 4. 2015 STD Treatment Guidelines: Anogenital Warts
#### Treatment of Internal Anogenital Warts

Internal anogenital warts include urethral meatus, vaginal, cervical, or intra-anal. Management of cervical warts or intra-anal warts should include consultation with a specialist.

<table>
<thead>
<tr>
<th>Recommended for Urethral Meatus Warts</th>
<th>Cryotherapy with liquid nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care providers must be trained on the proper use of cryotherapy because over- and under-treatment can result in complications or low efficacy.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Urethral Meatus Warts</th>
<th>Surgical removal</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Recommended for Vaginal Warts</th>
<th>Cryotherapy with liquid nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of a cryoprobe in the vagina is NOT recommended because of the risk for vaginal perforation and fistula formation.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Vaginal Warts</th>
<th>Surgical removal</th>
</tr>
</thead>
</table>

<table>
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<th>Cryotherapy with liquid nitrogen</th>
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Recommended for Cervical Warts

**Surgical removal**

Management of cervical warts should include consultation with a specialist. For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade SIL must be performed before treatment is initiated. For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade SIL must be performed before treatment is initiated.

Recommended for Cervical Warts

**Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80-90% solution**

*A small amount should be applied only to the warts.*

Management of cervical warts should include consultation with a specialist. For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade SIL must be performed before treatment is initiated. For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade SIL must be performed before treatment is initiated.

Recommended for Intra-anal Warts

**Cryotherapy with liquid nitrogen**

Management of intra-anal warts should include consultation with a specialist. Health care providers must be trained on the proper use of cryotherapy because over- and under-treatment can result in complications or low efficacy.

Recommended for Intra-anal Warts

**Surgical removal**

Management of intra-anal warts should include consultation with a specialist.

Recommended for Intra-anal Warts

**Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80-90% solution**

*A small amount should be applied only to the warts.*

Management of intra-anal warts should include consultation with a specialist.
