

# Human Papillomavirus Infection

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Module 2: [Self-Study Lessons 2nd Edition](#)

Lesson 5: [Human Papillomavirus Infection](#)

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## Introduction

Human papillomavirus (HPV) is a small, non-enveloped, double-stranded DNA virus that has oncogenic potential ([Figure 1](#)).<sup>[1]</sup> Most HPV infections, whether caused by low-risk or high-risk types, are transient, asymptomatic, and have no clinical consequences.<sup>[2]</sup> In a substantial number of individuals, however, sexually transmitted HPV infection may cause anogenital warts, oropharyngeal cancers, and urogenital cancers.<sup>[3,4]</sup> In the United States, approximately 45,000 HPV-related cancers are diagnosed each year, with cancer of the cervix the most common among women and cancer of the oropharynx the most common in men ([Figure 2](#)).<sup>[4]</sup> The 9-valent HPV vaccine is highly effective in preventing urogenital cancers and anogenital warts. Screening for HPV-related cervical cancer is an important component of cancer prevention for adult women. The following discussion on HPV will focus primarily on the diagnosis and management of anogenital warts, use of HPV vaccine to prevent urogenital cancers, and screening for HPV-related cancers.

## Epidemiology in the United States

### HPV Incidence

It is estimated that most sexually active men and women will acquire genital HPV infection at some point in their lives, but approximately 90% of these infections are clinically silent, and most infections resolve spontaneously.[1] Because HPV infection is not reportable in the United States, precise yearly statistics on the incidence (new HPV infections) are not available. Nevertheless, using the HPV Agent-based Dynamic model for Vaccination and Screening Evaluation (HPV-ADVISE), the Centers for Disease Control and Prevention (CDC) estimated that approximately 13 million new HPV infections in the United States occurred in 2018, including 6.9 million new HPV infections in men and 6.1 million in women (Figure 3).[5]

### HPV Prevalence

Using data from the 2013–2016 National Health and Nutrition Examination Survey (NHANES), there was an estimated 77.3 million persons in the United States with a prevalent HPV infection in 2018, including 42.5 million with a disease-associated HPV infection; the number of prevalent HPV infections was higher in men than in women (Figure 4).[5] Overall, the prevalence of any HPV type among persons aged 15 to 59 years in the United States was 40% (38.4% in cervicovaginal samples in women and 41.8% in penile samples in men).[5] In a review of 53 studies that addressed anal HPV prevalence in men who have sex with men (MSM), investigators found a pooled anal HPV prevalence for any HPV type was 63.9% for MSM without HIV and 92.6% for MSM with HIV.[6] In one international study that included participants from the United States, the anal HPV prevalence was 12.2% among HIV-negative men who have sex with women.[7] A meta-analysis of 95 studies found that anal HPV prevalence among women with normal anal cytology was 42% for women without HIV and 59% for women with HIV.[8] The prevalence of oral HPV is lower than with anogenital HPV. In a cross-sectional study conducted as part of the National Health and Nutrition Examination Survey (NHANES) in 2009–2010, the prevalence of any oral HPV type among men and women aged 14–69 years in the United States was 6.9% and for HPV-16 it was 1.0%.[9] In more recent NHANES data from 2011–2014 that evaluated adults 18 to 69 years of age, investigators reported the overall prevalence of any oral HPV infection in men (11.5%) was higher than in women (3.2%).[10]

### Prevalence of HPV-Related Diseases

The following summarizes major diseases related to sexually transmitted HPV. The incidence and prevalence of anogenital warts are difficult to estimate in the United States since diagnoses of anogenital warts are not reportable. Data for cervical and anal cancer come from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program.[11]

- **Anogenital Warts:** Most available prevalence data are based on selected analyses from urban sexually transmitted diseases clinics. For example, a 2010–2011 STD clinic-based study reported the prevalence of anogenital warts in 2010–2011 was 7.5% among men who have sex with women only, 7.5% among MSM, and 2.4% among women.[12]
- **Oropharyngeal Cancer:** In the United States, the number of new cases of HPV-associated oropharyngeal cancer has increased in recent years and these cancers are now the most common HPV-related cancer. In the United States, based on data from 2013 to 2017, there were an average of 19,775 HPV-related cancers of the oropharynx each year in the United States, with 16,245 (82%) of these occurring in men and 3,530 (18%) in women.[4]
- **Cervical Cancer:** In the United States for 2021, the NCI SEER Program estimates there will be 14,480 new cases of cervical cancer and 4,290 deaths.[13] During the years 2014–2018, the median age of cervical cancer diagnosis in the United States was 50 years.[13] In 2018, the rate of cervical cancer was 7.0 per 100,000 persons.[13]
- **Anal Cancers:** In the United States for 2021, the NCI SEER Program estimates there will be 9,090 new cases of anal cancer and 1,430 deaths.[14] During the years 2014–2018, the median age of anal

cancer diagnosis in the United States was 63 years.[14] In 2018, the rate of anal cancer was 1.8 per 100,000 persons.[14]

## **Factors Associated with HPV Infection**

Key factors associated with acquisition of genital HPV infection include higher number of lifetime sex partners and younger age of sexual debut.[15] Although a greater number of lifetime sex partners is associated with a higher likelihood of acquiring HPV, even a person with a few or even one lifetime sex partner can develop HPV infection.[3] For HPV-related oropharyngeal cancers, the risk is specifically related to oral sex. Investigators have evaluated potential risk factors associated with cervical cancer, including immunosuppression, long-term oral contraceptive use, multiple pregnancies, tobacco smoking, and coinfection with HIV, herpes simplex virus 2, or *Chlamydia trachomatis* infection.[16,17]

## **Cost**

In the United States, the total lifetime medical costs associated with HPV infection that was acquired in the year 2018, including costs for treatment of genital warts, precancers and cancers, was estimated to be \$755 million.[18]

# Microbiology, Pathogenesis, and Transmission

## Viral Structure

Human papillomavirus is a small, non-enveloped, double-stranded DNA virus that is approximately 50 to 60 nm in diameter.[19,20] 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 that are involved in viral assembly.[19,20] Human papillomavirus has a characteristic icosahedral viral outer shell, primarily comprised of 72 star-shaped pentameric capsomeres (Figure 5).[19,21] Each pentameric capsomer contains 5 HPV L1 proteins (Figure 6), and each virion contains 360 of the L1 proteins.[2] The 72 pentameric capsomeres have the unique ability to self-assemble and form the outer HPV shell; this self-assembling property is the key element used in the design and production of the self-assembling HPV vaccine.[22] The viral shell also contains up to 72 molecules of the L2 minor protein, which are believed to play a role linking the capsid to the HPV DNA.[2,23]

## Classification of HPV Types

The identification and typing of HPV in tissues occurs via the detection of HPV DNA or HPV mRNA. More than 200 types of HPV have been classified, and more than 40 types of HPV can infect the genital tract of humans.[19,24,25] The genital HPV types, which have a specific affinity for genital skin and mucosa, are divided into two groups based on whether they have an association with cancer: low-risk (nononcogenic types) and high-risk (oncogenic types) (Table 1).[19,26]

- **Low-Risk HPV Types:** Infection with low-risk types (nononcogenic) can cause genital warts and benign or low-grade cellular changes.[1] An estimated 90 to 95% of anogenital warts are caused by HPV types 6 or 11, or a combination of both.[27,28,29]
- **High-Risk HPV Types:** Infection with high-risk types (oncogenic) can cause low-grade cervical cellular changes, high-grade cervical cellular changes (moderate to severe Papanicolaou [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.[30] A total of 12 HPV types have been identified as high-risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, with 2 additional types (68 and 73) considered as possibly cancer causing. Most HPV-related cancers are caused by HPV types 16 or 18, and approximately 65-70% of cervical cancers are caused by HPV types 16 or 18. In addition, about 10% of HPV-related cancers are caused by HPV types 31, 33, 45, 52, and 58.[2][Q] HPV Types and Cancer

## Pathogenesis

The HPV types that infect humans have a known specificity for mucosal and cutaneous epithelium.[19,31] Infection with HPV occurs at the basal cell layer of stratified squamous epithelial cells.[31] Infection stimulates cellular proliferation in the epithelium, and the infected cells display a broad spectrum of changes, with a spectrum of cellular outcomes that include inapparent infection, benign hyperplasia (papilloma), oncogenic progression, and invasive carcinoma.[31] 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.[32] The E7 protein binds to a tumor suppressor protein—the retinoblastoma protein—and inhibits its function.[33] The E6 and E7 proteins mediate much of the HPV oncogenic potential by assisting the cell in evading host immunity, a process that facilitates virion production in differentiating epithelial cells.[2,31]

## Transmission of Genital HPV

Transmission of genital HPV is predominantly associated with sexual activity that results in friction-induced microabrasions during skin-to-skin contact.[2,27] Transmission rates of HPV between sex partners are high,

and transmission often occurs from persons with HPV who are asymptomatic or have subclinical infection.[34,35] Consistent and correct use of condoms reduces the risk for genital HPV acquisition or transmission, and therefore reduces the risk for HPV-associated diseases.[3,36] Condom use, however, does not entirely prevent transmission of HPV, since exposure to HPV can occur in areas that are not fully covered or protected by a condom.[3] Treatment of warts or cervical cellular abnormalities will reduce, but not eliminate, the risk of transmission. Transmission of HPV through nonsexual routes can occur, but is uncommon.[37,38] Mothers with low-risk genital HPV types can rarely transmit HPV to their newborn during delivery, but if transmission does occur, HPV has the potential to cause recurrent respiratory papillomatosis in children.[39,40]

[Q] Transmission of HPV

## Natural History of HPV Infections

Available data, primarily from cervical HPV natural history, suggest that more than 90% of individuals with genital HPV infections are asymptomatic and clear the infection within 3 years.[2,41,42] The “viral clearance” can entail complete elimination of HPV from the tissues or cell-mediated immune suppression of the HPV to such a low level that HPV DNA levels are undetectable using sensitive HPV DNA tests (referred to as “viral latency”).[2,43]

- **Natural History with Anogenital Warts:** Nearly all anogenital warts are caused by HPV type 6 or 11, and longitudinal studies show warts develop in 14.6 to 64.2% of persons following acquisition of either of these HPV subtypes.[44,45,46] For individuals who go on to develop anogenital warts, the median incubation period, representing the time from acquisition to clinical manifestations, is approximately 2.9 to 6.0 months in women and 11.0 months in men.[28,45,46]
- **Natural History with Cervical HPV Infection:** Following acquisition of HPV, the median duration of HPV infection of the cervix (measured by detection of HPV DNA) is approximately 1 to 2 years, depending on the HPV type.[47] For women who develop cervical cancer, the time from infection until precancerous cytologic abnormalities develop is typically several years, and if progression to cervical cancer occurs, it typically does not occur until decades after the initial infection.[2,48,49] 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 7).[48,49,50,51]
- **Natural History with Anal HPV Infection:** Following acquisition of HPV, the median duration of HPV infection of the anus is highly HPV type-dependent. In one study involving young women with anal HPV, by 3 years clearance of anal HPV had occurred with 82.5% of non-16 high-risk HPV, 82.6% of low-risk HPV, 76.2% of HPV-16, and 36.4% for all HPV types.[52] In two separate studies involving MSM with HPV infection, there were median durations of HPV-16 infection of 17 and 22 months, respectively.[53,54] Precancers of the anus may also spontaneously regress, with one study finding a regression rate of 22 per 100 person years.[55]
- **Natural History with Oral HPV Infection:** The natural history of oral HPV infection is not well understood. In one study of immunocompetent men, oncogenic-type oral HPV infection cleared within 12 months.[56] Precursor lesions for HPV-associated oropharyngeal cancer have not been identified.

[Q] Natural History of HPV Infection

# 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. Persons with clinically evident disease have a range of possible presentations that correlate with the HPV type and host factors.[57] The three most common clinically significant manifestations associated with HPV infection are anogenital warts, oropharyngeal cancer, cervical cancer, cervical dysplasia, anal cancer, and anal dysplasia.[4,58] Although most precancerous lesions are not visible clinically, some will subsequently progress to form visible lesions or masses in the cervix or perianal region.

## Anogenital Warts

### Types of Anogenital Warts

Individuals with visible anogenital warts frequently have simultaneous infection with multiple HPV types. Anogenital warts can be confused with other conditions, including other genital infections, acquired dermatologic conditions, normal anatomic variants, and external genital squamous intraepithelial lesions. (Table 2) There are four major morphologic types of anogenital warts commonly described:

- 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 keratosis)

### Sites for Anogenital Warts

Anogenital warts commonly occur in areas of coital friction. For women, external warts can appear on the vulva, vaginal introitus, perineum, and perianal area; women can develop internal warts involving the vagina, cervix (Figure 8), or anal mucosa. In women, external genital warts are more common than vaginal and cervical warts. Intra-anal warts are seen predominantly in persons with a history of receptive anal intercourse. Perianal and intra-anal warts do not necessarily imply anal intercourse as they may develop secondary to autoinoculation, sexual activity other than anal intercourse, or spread from a nearby genital site. For men, anogenital warts may include external warts on the penis, urethral meatus, scrotum, perineum (Figure 9), perianal area (Figure 10), and anal canal (Figure 11).

### Symptoms Associated with Anogenital Warts

Most often, genital warts cause minimal symptoms except for cosmetic concerns.[59] Vulvar warts may cause dyspareunia, pruritus, or bleeding. 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.

[Q] Clinical Presentations of Anogenital Warts

### 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 sexually transmitted infections (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.

## **Cervical Dysplasia and Cervical Cancer**

Cervical dysplasia or cervical cancer may occasionally be apparent on physical examination with visual inspection of the cervix, but typically the visualization of dysplasia or early cancer requires additional modalities. Cervical cellular abnormalities are usually subclinical, and lesions associated with these abnormalities can be detected by Pap test or colposcopy, with or without biopsy of the lesion. Low-grade cervical cellular abnormalities often regress spontaneously without treatment. Even high-grade cervical intraepithelial neoplasia (CIN) may regress without treatment, particularly for younger women (aged 21-24 years) so treatment recommendations vary according to age at CIN diagnosis.[60]

## **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.[61] 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. High-grade anal intraepithelial neoplasia (AIN) may regress without treatment; younger men, those with AIN2 versus AIN3, and those with smaller lesions are more likely to regress.

## **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 12).[30,62]



## Diagnosis and Screening Tests

### Anogenital Warts

Although most cases of anogenital warts are diagnosed clinically, confirmation by biopsy may be needed in any of the following situations:[63]

- The lesions are atypical (e.g. pigmented, indurated, affixed to underlying tissue, bleeding, or ulcerated).
- The diagnosis is uncertain.
- The person with the anogenital warts is immunocompromised (including individuals with HIV).
- The lesions do not respond to therapy.
- The lesions worsen during treatment.

Application of acetic acid to suspected wart lesions is not routinely recommended due to its low specificity (many false-positives). External genital warts are not an indication for type-specific HPV DNA testing since this information does not alter the management.[63]

[Q] Indications for Biopsy of an Anogenital Wart

### Cervical Cancer and Cervical Dysplasia

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 and to confirm cervical cancer.

### Cervical Cancer Screening Tests

#### Cervical Cytology

The Pap test is the main screening test used to detect cervical cytologic abnormalities. The basic principle of the Pap test is to collect cervical cells and examine these cells under a microscope for any evidence of abnormal morphology. The Pap test requires collection of cells from the external surface of the cervix (ectocervix) and the canal of the cervix (endocervix); obtaining cells from the endocervix is particularly important to evaluate the squamocolumnar junction (transformation zone) region, since this region has the highest risk for development of cervical cancer. Collection devices used include wooden and plastic spatulas for ectocervical samples, and brushes and brooms for endocervical samples. The Pap test can be performed using either the conventional method (sample is collected, smeared on a glass cytology slide, and then fixed with a preservative) or liquid-based tests (the spatula or brush is directly placed in liquid collection medium).[64] The 2021 STI Treatment Guidelines also recommend the following considerations related to performing Pap tests and HPV tests:[65]

- Cervical cytology screening (e.g. Pap test) should not be considered a screening test for sexually transmitted infections.
- Liquid-based cytology is an acceptable alternative to conventional Pap tests, as it has similar test-performance characteristics.
- Ideally, the conventional cytology Pap test should be performed 10 to 20 days after menses, whereas liquid-based Pap testing can be performed any time during the menstrual cycle.
- 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 STI testing can be collected first.
- 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 samples from the cervical transformation zone (e.g. cytobrushes) improves the accuracy of Pap tests.

## HPV Testing

The HPV tests are molecular-based tests that can confirm the presence of HPV by detecting viral DNA or mRNA. In the United States there are several HPV tests that are FDA-cleared for use, but only for testing of cervical specimens. The HPV tests vary from those that detect only the highest risk oncogenic HPV types (16 and 18) to assays that detect a full array of oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). The HPV assays that specifically detect oncogenic HPV types are sometimes referred to as high-risk HPV (hrHPV) tests. Primary HPV testing is the term used to describe HPV testing alone (without cytology testing). In the United States, there are two HPV tests FDA-cleared for primary HPV testing and five HPV tests approved for cotesting.[66] The main use for HPV testing is for cervical cancer screening and as a component of follow-up testing in women with abnormal Pap smear results. Note that HPV testing is NOT recommended in the following situations:[65]

- Deciding whether to vaccinate against HPV
- Conducting HPV tests for low-risk (nononcogenic) HPV types (e.g. types 6 and 11)
- Providing care to persons with genital warts or their partners
- Testing persons aged younger than 25 years as part of routine cervical cancer screening
- Testing oral or anal specimens

## Cotesting

When HPV testing is performed with cytology (Pap smear), it is referred to as cotesting. Multiple studies have shown that combined Pap and HPV testing, when compared with either test alone, increases the rate of detection of grade 2 or 3 cervical intraepithelial neoplasia.[67,68,69] Cotesting can be performed on the same sample or on separate samples.

## Nomenclature for Interpretation of Cervical Cancer Screening Tests

Multiple different types of classification systems have been used to report and describe findings on cervical cancer screening results.[2] The major categories used for interpretation are cytology and histology.

- **Cytology:** The major systems used for cytologic scoring in the United States are the original Papanicolaou (Pap) scoring system and the more recent Bethesda scoring.
  - **Pap Scoring System:** The Pap scoring system in which severity (I-V) is typically graded based on the degree of cytological atypia (abnormal mitotic figures and changes in nuclear shape and size) and the loss of cervical cell cytoplasmic maturation.
  - **Bethesda Scoring System:** The Bethesda scoring system is the major cervical cytology scoring system used in the United States. The Bethesda classifies squamous precursor lesions as low-grade squamous intraepithelial lesions (LSILs) or high-grade squamous intraepithelial

lesions (HSILs). Similar to the Lower Anogenital Squamous Terminology (LAST) histology scoring system, it incorporates LSIL and HSIL, but it also includes the designations negative for intraepithelial lesion and malignancy (NILM) and atypical squamous cells of undetermined significance (ASC-US), for an equivocal abnormality.[70]

- **Histology:** The two major histology systems used in cervical cancer screening are the cervical intraepithelial neoplasia (CIN) scale and the Lower Anogenital Squamous Terminology (LAST) scale.[2]
  - **CIN:** The CIN scale is used for squamous lesions and is based on the fraction of normal epithelial cells replaced by undifferentiated cells; the CIN categories include CIN1 (formerly called mild dysplasia), CIN2 (previously called moderate dysplasia), and CIN3 (previous terms were severe dysplasia and carcinoma in situ). Lesions that are CIN3 are considered premalignant with a potential to progress to invasive cancer.
  - **LAST:** The LAST scale also is used for squamous lesions, and it consists of a two-tiered system that classifies squamous precursor lesions as low-grade squamous intraepithelial lesions (LSILs) or high-grade squamous intraepithelial lesions (HSILs). Lesions that were previously classified as CIN1 correspond to cervical LSILs and CIN3 lesions correspond to cervical HSILs. Due to the poor reproducibility of CIN2, the differentiation between LSIL and HSIL is made based on immunohistochemical staining of biomarker p16 (a progression-related biomarker).[71,72] For CIN2 lesions that have a negative p16 staining are downgraded to LSIL, whereas p16 positive CIN2 lesions are considered HSIL. The LAST nomenclature system is preferred as it better reflects the current knowledge of HPV infection biology.

## Anal Cancer Detection and Screening Tests

### Digital Anorectal Exam (DARE)

In persons with HIV and men who have sex with men (and have receptive anal intercourse), a digital anorectal examination on a yearly basis is recommended by some experts, with the goal of detecting early anal cancer.[73,74,75] This examination is performed by inserting a gloved finger (with lubricant) into the anus to gently palpate for abnormalities.[76] The digital anorectal examination does not require special training or special equipment other than gloves and lubricant. Note that if anal cytology is planned, it should be performed prior to the digital anorectal examination since lubricant should not be in the anal canal when anal Pap testing is performed.[76,77]

### Anal Cytology

Although the same general principles related to cervical Pap testing apply to anal Pap testing, several key aspects of obtaining the clinical sample for the anal Pap should be highlighted.[76,77]

- The person undergoing the testing should receive instructions not to place anything in their anus for at least 24 hours, including avoiding anal enemas or douching.
- Lubricants should not be used when performing the anal Pap.
- The swab used for the anal Pap should be synthetic (rayon or polyester) and moistened with tap water prior to the procedure.
- To collect the anal cytology sample, insert the swab 2 to 3 inches into the anal canal; the swab should then slowly be withdrawn over a period of 15 to 30 seconds while using a spiral motion to sample the anal canal circumference.
- Smear the swab on a glass slide (conventional cytology) or place the swab in liquid media (liquid-based cytology); either of these methods is acceptable when performing anal Pap testing.

### Anal HPV Testing

The HPV tests are not FDA-approved for use on anal specimens. In addition, these tests are not considered useful for anal cancer screening because of the high prevalence of anal HPV in men who have sex with men—the population at highest risk for anal cancer.[65]

## High-Resolution Anoscopy

High-resolution anoscopy is the process of examining the anal canal and perianal region with a colposcope (to provide lighting and magnification) in conjunction with repeated application of acetic acid and Lugol's iodine solution (to identify lesions in the anal epithelium) during the procedure.<sup>[78]</sup> The goal of this office-based procedure is to visualize the entire anal canal and perianal region.<sup>[78]</sup> High-resolution anoscopy should only be performed by persons who have received adequate professional training on performing this procedure and in performing anal biopsies.<sup>[78]</sup> Routine use of high-resolution anoscopy as a primary screening tool for anal cancer is not recommended. Programs that perform anal cytology testing should ideally have good access to high-resolution anoscopy for evaluation of persons who have an abnormal anal Pap. High-resolution anoscopy provides an effective option for diagnosing superficially invasive squamous carcinoma, detecting high-grade anal dysplasia ([Figure 13](#)), and managing the precancerous anal intraepithelial neoplasia.<sup>[65,79,80]</sup>

## Reporting and Public Health Follow-Up

HPV infection is not reportable in any state.

# Screening Recommendations for HPV-Related Cancers

## Cervical Cancer Screening

There is ample evidence for the effectiveness of screening for HPV-associated precancers for women. In recent years, there has been a move from multiple organizations to consolidate and align cervical cancer screening recommendations. To this end, 2018 United States Preventive Services Task Force (USPSTF) Cervical Cancer Screening Recommendations have now been formally endorsed by the American College of Obstetricians and Gynecologists (ACOG), the Society of Gynecologic Oncology (SGO), and the American Society for Colposcopy and Cervical Pathology.[\[81\]](#)

## USPSTF Cervical Cancer Screening Recommendations

The following summarizes key elements in cervical cancer screening recommendations from the 2018 United States Preventive Services Task Force (USPSTF).[\[82,83\]](#) Note the USPSTF gives an “A” rating for cervical cancer screening in women 21–65 years of age.[\[82,83\]](#)

- **Type of Screening:** The cervical cytology (Pap test) screening should be performed using either conventional or liquid-based cytologic tests. The HPV testing should utilize one of several FDA-cleared oncogenic or high-risk HPV tests.
- **Age for Conducting Screening:** Routine cervical screening should be performed starting at age 21 years and continue through age 65 years.
- **Women 21 through 29 Years of Age:** For women 21–29 years of age, cervical cytology screening is recommended every 3 years.
- **Women 30 through 65 Years of Age:** For women 30–65 years of age, cervical cancer screening includes three options: cervical cytology alone every 3 years, high-risk HPV testing alone every 5 years, or cervical cytology in combination with high-risk HPV testing every 5 years.
- **Women Older than 65 Years of Age:** Cervical cancer screening is not recommended in women who are older than 65 years of age who have had adequate prior cervical cancer screening and who are not at high risk for cervical cancer.
- **Healthy Women and Girls Younger than 21 Years of Age:** Cervical cancer screening is not recommended for women and girls younger than 21 years of age.
- **Women with Hysterectomy:** Cervical cancer screening is not recommended for women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade cervical precancerous lesion or cervical cancer.
- **Prior HPV Immunization:** Recommendations for cervical screening should not be determined by prior receipt of HPV vaccine.

## American Cancer Society Cervical Cancer Screening Recommendations

The following summarizes key elements in cervical cancer screening recommendations from the American Cancer Society for individuals who have a cervix.[\[66\]](#)

- **Age for Conducting Screening:** Routine cervical screening in women should be performed starting at age 25 years and continue through age 65 years.
- **Type of Screening:** For women aged 25–65 years of age, screening should consist of primary HPV testing every 5 years. If primary HPV testing is not available, there are two screening options: (1) cotest with an HPV test and a Pap test every 5 years or (2) a Pap test alone every 3 years. Note that a primary HPV test is considered a standalone HPV test.
- **Screening for Women 65 Years of Age and Older:** Cervical cancer screening is not recommended in women who are older than 65 years of age who had screening in the prior 10 years with normal results and no history of CIN2 (or more serious diagnosis) in the past 25 years.
- **Women with Prior Complete Hysterectomy:** Cervical cancer screening is not recommended for

women who have undergone total hysterectomy (removal of uterus and cervix), unless the procedure was performed for treatment of cervical cancer or serious cervical precancer. In addition, women who previously had a supra-cervical hysterectomy should continue cervical cancer screening using age-based recommendations.

- **Women with Prior Precancer:** For women previously diagnosed with a cervical precancer, screening should continue for at least 25 years, even if this extends past 65 years of age.
- **Screening for Women who are Immunosuppressed:** For women who are immunosuppressed, including persons with HIV, cervical cancer screening may need to occur more frequently than the recommended intervals.
- **Prior HPV Immunization:** Recommendations for cervical screening should not be determined by prior receipt of HPV vaccine; screening should follow age-specific screening recommendations.

### Screening for Cervical Cancer in Women who are Pregnant

Screening for cervical cancer in pregnant women should be 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

Several studies have documented an increased risk for cervical precancers and cancers in women with HIV.<sup>[84]</sup> Prior guidance suggested initiating screening within 1 year of onset of sexual activity, even in women younger than 21 years of age. In the recent HIV/AIDS Cancer Match Study, which was conducted during 2002–2016, there were no cases of cervical cancer in women younger than age 25 years.<sup>[85]</sup> Accordingly, the recommendation for the age onset of cervical cancer screening for women with HIV has changed and is now age 21 years, which is consistent with USPSTF recommendations for women without HIV.<sup>[75,82]</sup> The following summarizes cervical cancer screening recommendations for women with HIV.<sup>[75]</sup>

- **Age for Conducting Screening:** Women with HIV should receive baseline cervical cancer screening starting at 21 years of age. Cervical cancer screening in women with HIV should continue throughout their lifetime and not end at 65 years of age.
- **Women Younger than 30 Years of Age:** For women with HIV younger than 30 years of age, cervical cytology screening (Pap test) is recommended. If the initial Pap test is normal, then follow-up Pap testing should be performed in 12 months. 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, cotesting (Pap test and HPV test) is not recommended.
- **Women 30 Years of Age and Older:** For women with HIV 30 years of age and older, the acceptable screening options are Pap testing alone or cotesting (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. If the results of 3 consecutive Pap tests are normal, then follow-up Pap testing should be every 3 years. If cotesting is done at the time of diagnosis and the results are normal, then the next screening for cervical cancer should be performed in 3 years. Women with a normal Pap test but a positive HPV test should have cotesting repeated in 1 year; if either cotest is positive, then referral for colposcopy is recommended. In addition, if initial HPV testing is performed and is positive for HPV 16 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 the woman's age, Pap test results, high-risk HPV testing, and pathology from any biopsy samples. High-risk HPV DNA cotesting 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 lesson, but is addressed in detail in the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening

Tests and Cancer Precursors.[86]

## Screening for Anal Cancer

Data are insufficient to recommend routine anal cancer screening with anal cytology in women, men who have sex with women, MSM, and persons with HIV.[65] Evidence is limited on the natural history of anal intraepithelial neoplasia, reliability of screening methods, safety and response to treatments, and programmatic considerations.

- **Digital Anorectal Examination (DARE):** An annual digital anorectal examination may be useful to detect masses on palpation that could be anal cancer in persons with HIV as well as in MSM without HIV.[65,74]
- **Anal Cytology (Pap):** Some clinical centers perform anal cytology to screen for anal cancer among certain populations at increased risk for anal cancer (e.g. persons with HIV and MSM). For those with an abnormal cytologic result, follow-up high-resolution anoscopy is indicated. Initiating anal Pap screening should only be done if the center has developed a system to manage and follow those individuals with initial abnormal anal Pap smears, including performing high-resolution anoscopy and biopsy, when indicated.[65]
- **HPV Testing:** Anal cancer screening with HPV testing (high-risk HPV types) has a low clinical utility and is not recommended, primarily because of the high HPV prevalence among those populations at greatest risk for anal cancer, particularly MSM.[65]
- **High-Resolution Anoscopy:** For routine screening, high-resolution anoscopy is not recommended. It is only recommended as a component of management in persons who have an abnormal anal cytology.

## Screening for Oropharyngeal Cancer

In the United States, routine screening for HPV-associated oropharyngeal cancer in asymptomatic adults is not recommended.[87]

# Treatment of Anogenital Warts

## Goals of Wart Treatment

The primary goal for the treatment of anogenital warts is the removal of visible warts.[63] Available therapies reduce but do not completely eliminate the risk of HPV transmission. In addition, there are no data that suggest treatment of genital warts impacts the subsequent risk of anogenital HPV-related cancer. Most individuals have fewer than 10 genital warts and a total wart area less than 1.0 cm<sup>2</sup>. Complications rarely occur if treatments for anogenital warts are properly employed. Treatment of anogenital warts typically produces a very good clinical response within 3 months.[63] Although appropriate treatment can induce wart-free periods, subsequent recurrences are common, with a 20 to 50% recurrence rate at 3 to 6 months post-treatment.[88] Reappearance of genital warts within the first several months usually indicates recurrence rather than reinfection. If left untreated, visible genital warts persist with or without proliferation, but some regress spontaneously. Because spontaneous resolution of anogenital warts can occur, some individuals may choose to defer treatment and await possible spontaneous resolution.

## Selection of Therapy for Anogenital Warts

Among recommended treatments, there is no evidence that any treatment is superior to others.[63] The choice of the specific treatment should depend on the location of anogenital warts, provider treatment experience, available therapies, preference of the person with the anogenital warts, and pregnancy status.[63] For persons desiring treatment of their anogenital warts, the major initial decision point is whether to utilize patient-applied or provider-administered therapy.[63] Although provider-administered therapies often result in more rapid resolution and require fewer treatments, many individuals prefer to self-apply therapy since this can be done in the privacy of their home and without having to make multiple clinic visits.[63] In general, warts with a relatively small area respond to a wide range of patient-applied and provider-administered treatment modalities, whereas treatment options with very large warts are limited, usually requiring provider-administered treatment. For provider-administered options, cryotherapy and surgical removal are feasible in all anatomic locations; trichloroacetic acid (TCA) or bichloroacetic acid (BCA) is acceptable for treatment of vaginal, cervical, and intra-anal warts; and the use of TCA, BCA, or podophyllin is contraindicated for urethral meatus warts.

[Q] Approach to Treatment of Anogenital Warts

## Therapy for External Anogenital Warts

Multiple patient-applied and provider-administered therapies are recommended as options for the treatment of external anogenital warts.[63] Medical providers should have appropriate knowledge and training for at least one provider-administered and one patient-applied treatment. Some clinicians will initiate therapy with a provider-administered option to make rapid initial progress in the treatment of warts and then transition to patient-applied therapy when the bulk of the warts have been significantly reduced. The following summarizes several recommendations for the use of patient-applied and provider-administered therapies for external anogenital warts (Table 3).[63]

- **Patient-Applied Therapies:** Recommended patient-applied options include imiquimod cream, podofilox (podophyllotoxin) solution or gel, and sinecatechins (green tea extract); all require repeated applications.
  - Imiquimod Cream: The imiquimod 5% cream should be applied to the warts 3 times per week at bedtime for up to 16 weeks, whereas the lower-strength imiquimod 3.75% cream requires application every night at bedtime for up to 8 weeks; with either cream, it should be left on the warts for 6-10 hours and then thoroughly washed off with soap and water. Irritation, burning, and pain are potential side effects of this topical treatment.
  - Podofilox: The podofilox 0.5% solution or gel should be applied to the warts in weekly cycles of



twice a day applications for 3 days followed by no treatment for 4 days; the solution should be applied with a cotton swab and the gel with a finger. When using podofilox, it is important that the total volume of podofilox not exceed 0.5 mL/day and the total wart area treated not exceed 10 cm<sup>2</sup>. The podofilox treatments can be given for up to 4 weekly cycles.

- Sinecatechins: The sinecatechins 15% ointment should be administered 3 times/day using a finger to apply a 0.5 cm strand of ointment to each anogenital wart; the goal is to cover the wart entirely with a thin layer of the sinecatechins. The ointment should not be washed off after application. Genital, anal, and oral sexual contact should be avoided while sinecatechins ointment is present on the skin. This treatment can be administered for up to 16 weeks. Treatment with sinecatechins is not recommended for persons with genital herpes or for immunocompromised persons, including those with HIV.
- **Provider-Administered Therapies:** Recommended treatments for anogenital warts administered by a medical provider include cryotherapy, surgical removal, and application of TCA or BCA.
  - Cryotherapy: This process uses application of liquid nitrogen to destroy the anogenital warts via thermal-induced cytolysis. Most clinicians can easily learn how to use cryotherapy for treatment of external anogenital warts, but appropriate training should include instruction on appropriate duration of freezing with each treatment. Post-treatment pain and blistering are common.
  - Surgical Removal: Only individuals who have received involved special training on surgical removal of anogenital warts should use this procedure. Multiple techniques can be employed including tangential scissor excision, tangential shave excision, curettage, laser, or electrocautery.
  - Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA): The application of TCA or BCA 80-90% solution should only be performed by an individual with training in this application and for treatment of small lesions. These acid agents destroy wart tissue by causing chemical coagulation of proteins. Only a small amount of the solution should be applied to the wart and the solution should dry before the patient moves. If too much is applied or the patient experiences pain, sodium bicarbonate (i.e. baking soda) can be applied to neutralize the acid; the sodium bicarbonate is typically applied as a liquid soap preparation or powdered with talc.

[Q] Patient Applied Therapy for Anogenital Warts

## 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.[63] Podophyllin resin 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.[89] 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

Internal anogenital warts, including warts located in the urethral meatus, vagina, cervix, or intra-anal region, are complicated to treat, and, in many instances, require management or consultation with a specialist (Table 4).[63] Although cryotherapy for intra-anal warts is listed as an option, many experts would only use cryotherapy for external anogenital warts.

## Genital Wart Follow-Up

Since post-treatment recurrences are common in persons with anogenital warts, a follow-up evaluation 3 months after treatment should be offered. Although post-wart treatment follow-up is not mandatory, it provides an opportunity to monitor for complications of therapy, check for recurrent lesions, document

absence of warts if this has occurred, and reinforce education and counseling messages. The presence of genital warts does not alter indications or frequency for cervical cytology screening.

## **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 safely used.[63] Cytotoxic agents (podophyllin, podofilox, imiquimod) should not be used during pregnancy.[63] 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, since it is unclear whether Cesarean delivery prevents respiratory papillomatosis among infants.[63]

[Q] Treatment of Anogenital Warts in Pregnancy

### **Management of Genital Warts in Immunocompromised Patients**

The general approach to the treatment of genital warts in persons with HIV is the same as for those without HIV.[63] Persons with HIV, 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 of HPV Infection

### Limiting Number of Sex Partners

Abstaining from sexual activity remains the most reliable method for preventing genital HPV infection.<sup>[63,65]</sup> Individuals can decrease their chances of infection by limiting their number of sex partners.<sup>[63,65]</sup>

### Condom Use

Consistent use of latex male condoms can reduce the risk of sexual HPV transmission.<sup>[3]</sup> For newly sexually active women, one study demonstrated consistent use of condoms by the male partner during vaginal intercourse resulted in a 70% reduction in risk of newly acquired cervical or vulvovaginal HPV infection when compared with male partners who used condoms only 5% of the time.<sup>[90]</sup> In addition, several studies involving sexually active men who have sex with women have shown an approximate 2-fold lower risk of HPV acquisition among those men who always used a condom when compared with those who never used condoms.<sup>[91]</sup> There are inadequate data to show benefit of condoms in preventing HPV among MSM.

### HPV Vaccines

The HPV vaccine is based on recombinant technology that produces L1 major proteins, which self-assemble into viral-like particles (Figure 14).<sup>[22]</sup> In the United States, three HPV vaccines (2vHPV, 4vHPV, and 9vHPV) have been licensed for use, but the 9vHPV is now the only available HPV vaccine. The 9vHPV, which was FDA-approved in 2014, 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.<sup>[92]</sup> Based on HPV typing data from samples taken from persons with HPV-associated cancers of the vulva, vagina, anus, penis, and oropharynx, the HPV types in 9vHPV overlap tightly with these cancer-causing HPV types (Figure 15).<sup>[30]</sup> The 9vHPV vaccine has shown excellent safety in females and males, with immediate post-injection syncope the only major associated adverse effect.<sup>[93,94]</sup>

[Q] Main Component of HPV Vaccine

### HPV Vaccine Recommendations

The goal of HPV vaccine is to prevent infection with all the HPV types in the 9vHPV vaccine and therefore reduce the risk of genital warts and HPV-related cancers. The potential role of the 9vHPV vaccine among unvaccinated individuals who are diagnosed with an HPV-related lesion or precancer is not known and studies are ongoing to address this issue. The following summarizes recommendations of the Advisory Committee for Immunization Practices (ACIP) for the use of the 9vHPV vaccine to prevent HPV infection.<sup>[95,96,97]</sup>

- **Age of Immunization and Age Range:** The 9vHPV should be administered routinely at age 11 or 12 years (can start at age 9 years). Individuals who do not receive 9vHPV by age 13 years can receive 9vHPV through age 26 years as a catch-up vaccination. Persons 27 through 45 years of age who have not previously received HPV vaccine should engage in shared decision-making with their clinician, as the public health benefit of 9vHPV in older individuals is not clear since many of these individuals have already acquired multiple HPV types.
- **Dosing Schedule:** For healthy individuals who initiate the vaccination at ages 9 through 14 years, the 2-dose HPV vaccine schedule is recommended (given at 0 and 6 months). Persons who start the series after 15 years of age require the 3-dose series (given at 0, 1-2 months, and 6 months).
- **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 too soon, then it should be repeated (at least 5 months after the first dose). For the 3-dose series, the recommended minimal interval is 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 repeated after another minimum interval has elapsed since the most recent dose.

- **Persons with Immunocompromising Conditions:** The 3-dose vaccine series should be used for persons with immunocompromising conditions, including HIV, malignant neoplasms, autoimmune disease, B lymphocyte antibody deficiencies, and T lymphocyte complete or partial defects, and receipt of transplantation or immunosuppressive therapy.
- **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.
- **Pregnancy:** The HPV vaccine is not recommended for use during pregnancy. If, however, it is inadvertently given to a pregnant woman, no interventions are required. In addition, pregnancy testing is not needed prior to administration of the HPV vaccine.
- **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.[97] 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.

[Q] Dosing Schedule for HPV Vaccine

## Impact of HPV Vaccine on HPV Prevalence

In the United States and in other countries, significant declines in vaccine-targeted HPV strains occurred within a decade of HPV immunization.[98,99,100] The NHANES registry has been used to longitudinally compare prevalence rates of vaccine-targeted strains (HPV 6, 11, 16, and 18) among females 14 to 34 years of age living in the United States.[101] When comparing prevalence rates for vaccine-targeted strains between the pre-vaccine era (2003-2006) and after 4 years of the 4vHPV vaccine (2009-2012), there was a 63% decrease in the prevalence of the 4vHPV types among females 14 to 19 years of age and a 35% decrease among females 20 to 24 years of age (Figure 16).[101] When extending these data analyses to 2015-2018, further declines in HPV prevalence rates were observed, with an overall decrease of 88% among females aged 14-19 years and 81% among those 20-24 years of age; declines in older women 25-34 years of age also occurred but were not as dramatic as in those younger than 25 years of age (Figure 17).[102] There are limited HPV prevalence data in males, but one study demonstrated a 59.4% reduction in persistent anal infections with HPV types 6, 11, 16, and 18 among MSM who had received the 4vHPV vaccine.[103] In addition, several countries with HPV vaccination coverage of 50% or greater have shown early evidence of vaccine cross-protection and herd immunity effects that favorably impact males.[104,105,106]

## Impact of HPV Vaccine on Anogenital Warts

In the United States, the trends for anogenital wart prevalence vary by age and sex. The initial declines were observed in 2007-2010 among females 15 to 19 years of age, followed by declines during 2009-2010 among females 20 to 24 years of age (Figure 18).[12] A subsequent study that included data out to 2014 showed continued declines in anogenital wart prevalence in women younger than age 25 and a new decline in women 25-29 years of age.[107] These data, taken together, correlate well with expected declines following the introduction of the 4vHPV vaccine in young females in 2006. Several 4vHPV vaccine trials have shown marked reductions in HPV-related anogenital lesions in female and male participants who received the HPV vaccine compared with those who received placebo.[108,109] In addition, data obtained from 27 clinics participating in the STD Surveillance Network showed an overall 47.1% decrease in anogenital warts during 2010-2016, including significant declines among women (62.2%), men who have sex with women (39%), and MSM (53.4%) (Figure 19).[110] In a meta-analysis involving data from high-income countries, the following major decreases were observed in the diagnosis of anogenital warts: 67% among girls aged 15 to 19 years, 54% among women aged 20 to 24 years, 31% among women aged 25 to 29 years, 48% among boys aged 15 to 19 years, and 32% among men aged 20 to 24 years.[106]

## **Impact of HPV Vaccine on Cervical Dysplasia and Cancer**

Because cervical cancer does not typically develop until at least 15 to 20 years after initial HPV infection and the 4vHPV vaccine was not widely used until after 2006, there are a limited number of studies demonstrating the effect of the HPV vaccine in lowering rates of cervical cancer. Nevertheless, early data from several studies strongly suggest that HPV vaccination markedly reduces risk for precancers and cancers of the cervix. In one meta-analysis, the authors concluded that after 5 to 9 years of HPV vaccination, CIN2+ detected on cervical screening decreased by 51% among girls aged 15 to 19 years and by 31% among women aged 20 to 24 years.[\[106\]](#) An analysis of the New Mexico HPV Pap Registry from 2007-2014 showed significant declines in all stages of cervical intraepithelial neoplasia for women 15 to 19 years of age.[\[111\]](#) Data from the CDC HPV-IMPACT Project, a sentinel surveillance project, also demonstrated dramatic declines in cervical precancer incidence from 2008-2012 for women 18 to 20 years of age.[\[112\]](#) The most robust data on vaccine-related prevention of cervical cancer is from a nationwide Swedish registry that followed 1,672,983 girls and women who were 10 to 30 years of age from 2006 through 2017 and found that participants who had initiated 4vHPV vaccination before the age of 17 years had an 88% lower risk of cervical cancer than participants who had never received the HPV vaccine.[\[113\]](#)

## **Impact of HPV Vaccine on Anal Cancer**

There are limited data on the impact of HPV vaccine on anal dysplasia and anal cancer. In a randomized 4vHPV vaccine trial that enrolled 602 healthy MSM who were 16 to 26 years of age, the rate of grade 2 or 3 anal intraepithelial neoplasias related to infection with HPV types 6, 11, 16, or 18 was 54.2% lower in the vaccine recipients than in participants who received placebo.[\[103\]](#)

## Counseling and Education

The 2021 STI Treatment Guidelines recommend the following key counseling and education messages for persons diagnosed with HPV infection.[3]

- Anogenital HPV infection is common. It usually infects the anogenital area but can infect other areas, including the mouth and throat. The majority of sexually active persons get HPV at some time during their lifetime, although most never know it.
- Partners tend to share HPV, and it is not possible to determine which partner transmitted the original infection. Having HPV does not mean that a person or his or her partner is having sex outside the relationship.
- Persons who acquire HPV usually clear the infection spontaneously, meaning that HPV becomes undetectable with no associated health problems.
- If HPV infection persists, genital warts, precancers, and cancers of the cervix, anus, penis, vulva, vagina, head, or neck might develop.
- Discussion of tobacco use, and provision of cessation counseling, is important because of its contribution to the persistent infection and progression of HPV-related precancers and cancers.
- Many types of HPV are sexually transmitted through anogenital contact, mainly during vaginal and anal sex. In addition, HPV might also be transmitted during oral sex and genital-to-genital contact without penetration. In rare cases, a pregnant woman can transmit HPV to an infant during delivery.
- Treatments are available for the conditions caused by HPV but not for the virus itself.
- Having HPV does not make it harder for a woman to get pregnant or carry a pregnancy to term. However, certain precancers or cancers that HPV can cause, and the surgical procedures needed to treat them, can affect a woman's ability to get pregnant or carry a pregnancy to term.
- No HPV test can determine which HPV infection will become undetectable and which will persist or progress to disease. However, in certain circumstances, HPV tests can determine whether a woman is at increased risk for cervical cancer. These tests are not for detecting other HPV-related problems, nor are they useful for women aged 25 years or younger or in men of any age.

## 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 transmission risk-reduction methods such as consistent and correct condom use. Partner counseling also provides an opportunity to offer these partners STI and Pap screening (if appropriate), as well as counseling on prevention. The following are the main counseling issues for sex partners of persons diagnosed with HPV infection.

- Watch for clinical recurrences (most frequently occurring in the first 3 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).
- Individuals with anogenital warts can still potentially transmit HPV to sex partners after visible warts are gone, since HPV can remain persistent in the tissues.
- The risk of transmitting HPV to sex 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.



## Summary Points

- Human papillomavirus (HPV) is one of the most common sexually transmitted infections with approximately 40 subtypes that can potentially cause anogenital infection. The HPV types are classified based on their oncogenic potential as either low-risk (nononcogenic) types or 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; 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.
- Treatment of anogenital warts includes multiple options that include patient-applied therapies and provider-administered therapies. Since there are no antiviral treatments that eradicate HPV, warts can recur after treatment.
- 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.
- Data are insufficient to recommend routine anal cancer screening, though some centers use anal cytology to screen populations at increased risk for HPV, including men who have sex with men and persons with HIV.
- Consistent and correct use of condoms reduces the risk for genital HPV acquisition or transmission but does not entirely prevent transmission of HPV.
- The 9-valent HPV vaccine (9vHPV) is now the only HPV vaccine available in the United States; this vaccine prevents infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.
- Use of the HPV vaccines has led to population declines in HPV prevalence, anogenital warts, and HPV-related precancers and cancers.

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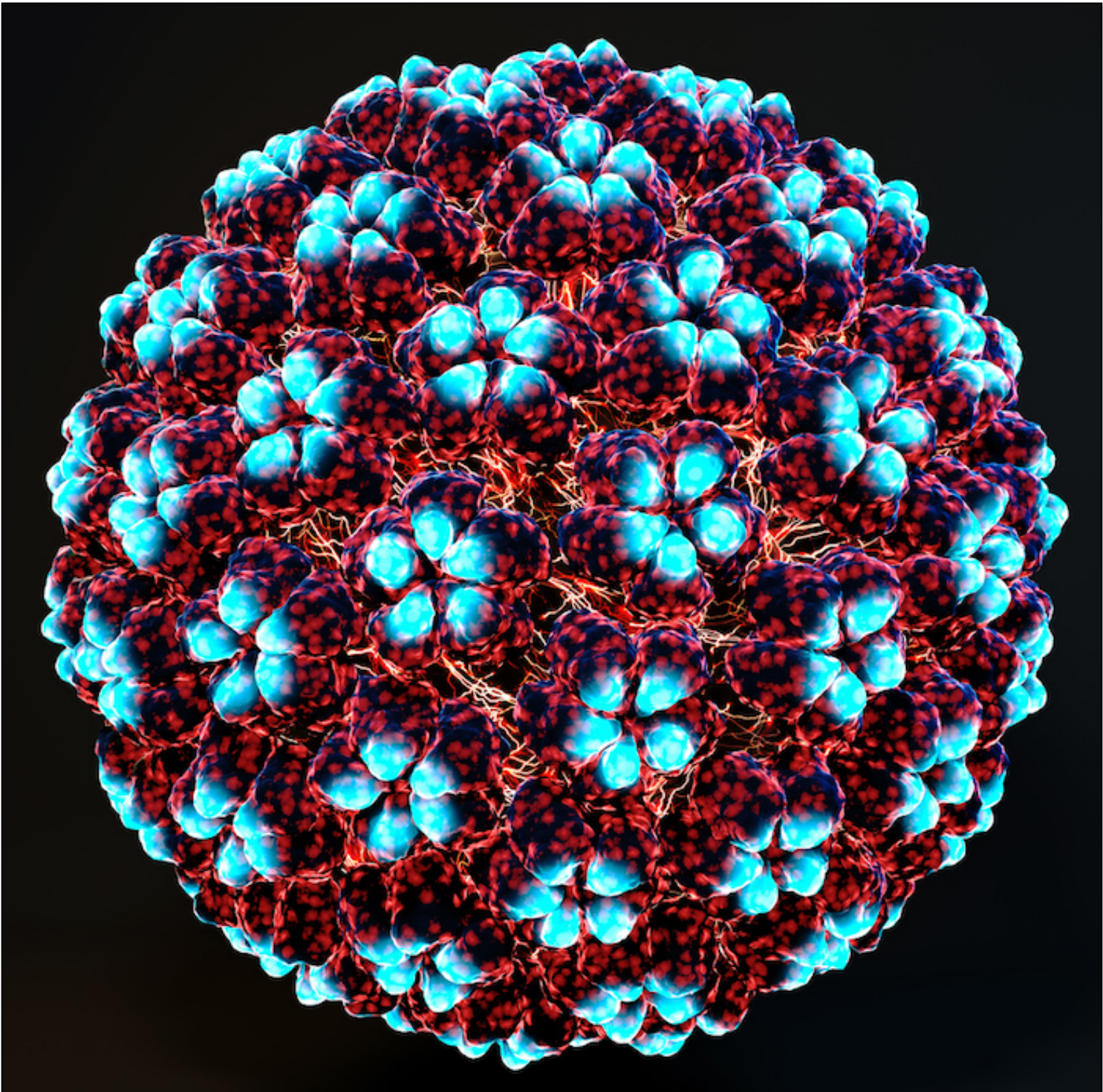
## Figures

### Figure 1 Human Papillomavirus

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 a 72 -pentameric capsomere (light blue).

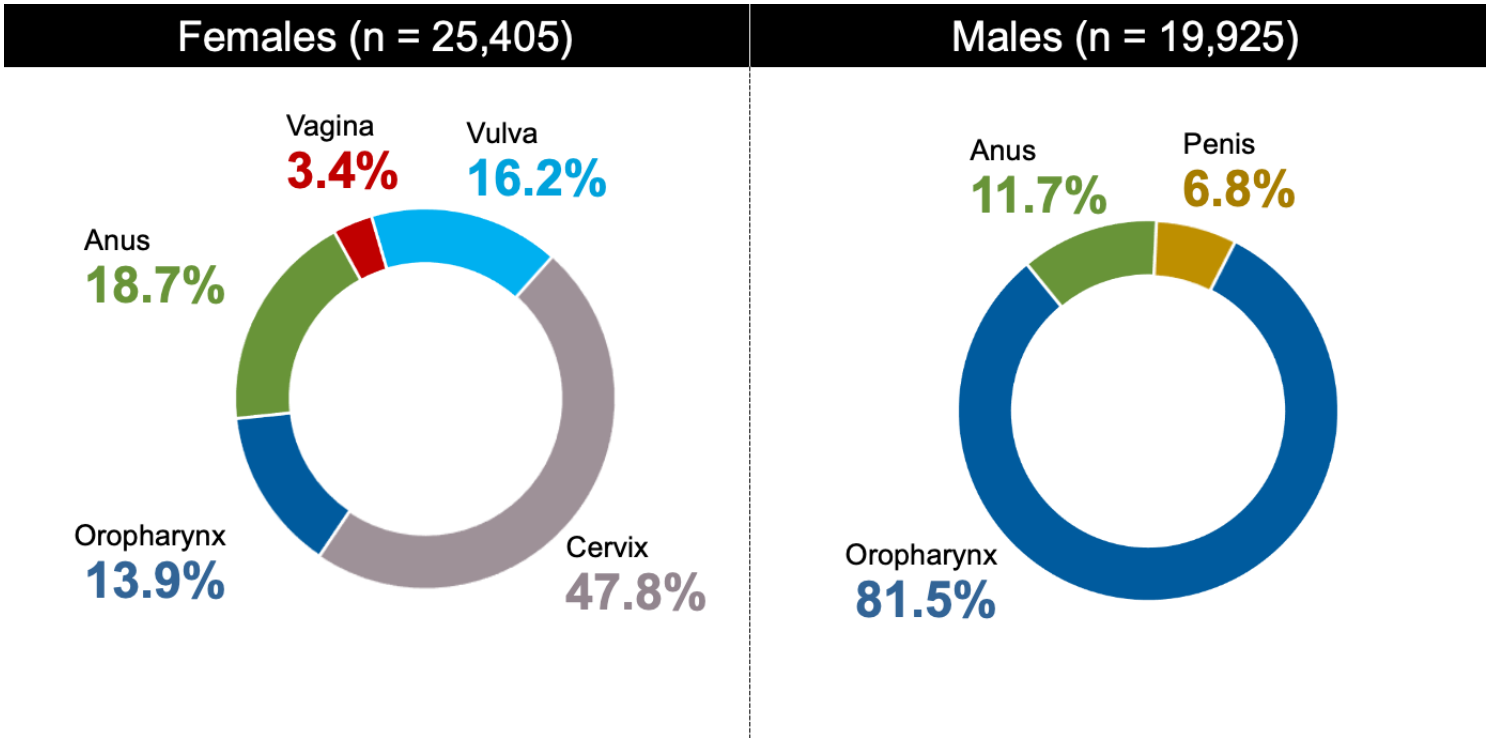
Illustration by 306/Shutterstock.com. Image used under license from Shutterstock.com.





**Figure 2 Cancers Associated with Human Papillomavirus, United States, 2013-2017**

Source: Centers for Disease Control and Prevention. Cancers Associated with Human Papillomavirus, United States—2013-2017. USCS Data Brief, no 18. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services;2020.

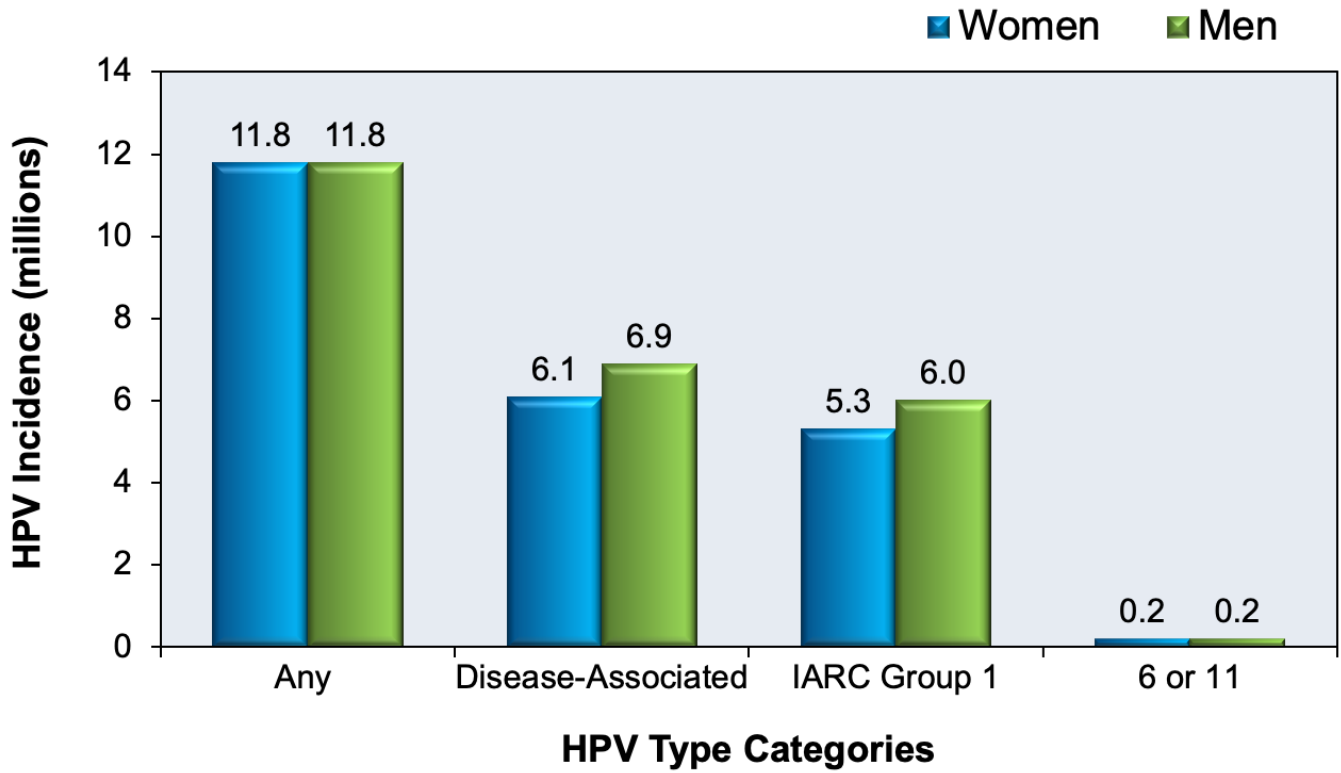




**Figure 3 Estimated HPV Incidence for Persons Aged 15-59 Years, United States, 2018**

Any HPV = any of 37 types detected using Linear ArrayIARC Group 1 = Twelve HPV types are defined by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (HPV 16/18/31/33/35/39/45/51/52/56/58/59)HPV 6/11 = noncarcinogenic HPV types that cause most genital warts

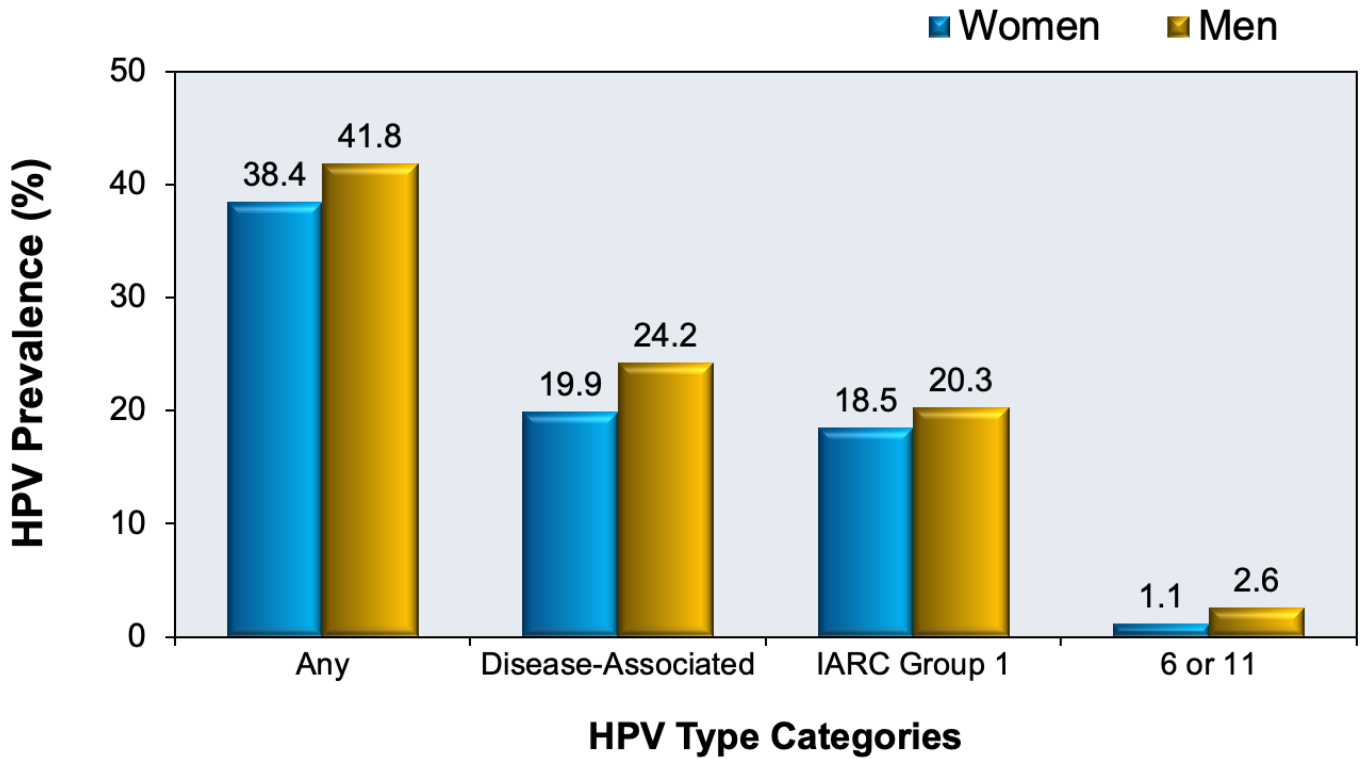
Source: Lewis RM, Laprise JF, Gargano JW, et al. Estimated Prevalence and Incidence of Disease-Associated Human Papillomavirus Types Among 15- to 59-Year-Olds in the United States. Sex Transm Dis. 2021;48:273-7.



**Figure 4 Estimated HPV Prevalence for Persons Aged 15-59 Years, United States, 2013-2016**

Any HPV = any of 37 types detected using Linear Array  
IARC Group 1 = Twelve HPV types are defined by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (HPV 16/18/31/33/35/39/45/51/52/56/58/59)  
HPV 6/11 = noncarcinogenic HPV types that cause most genital warts

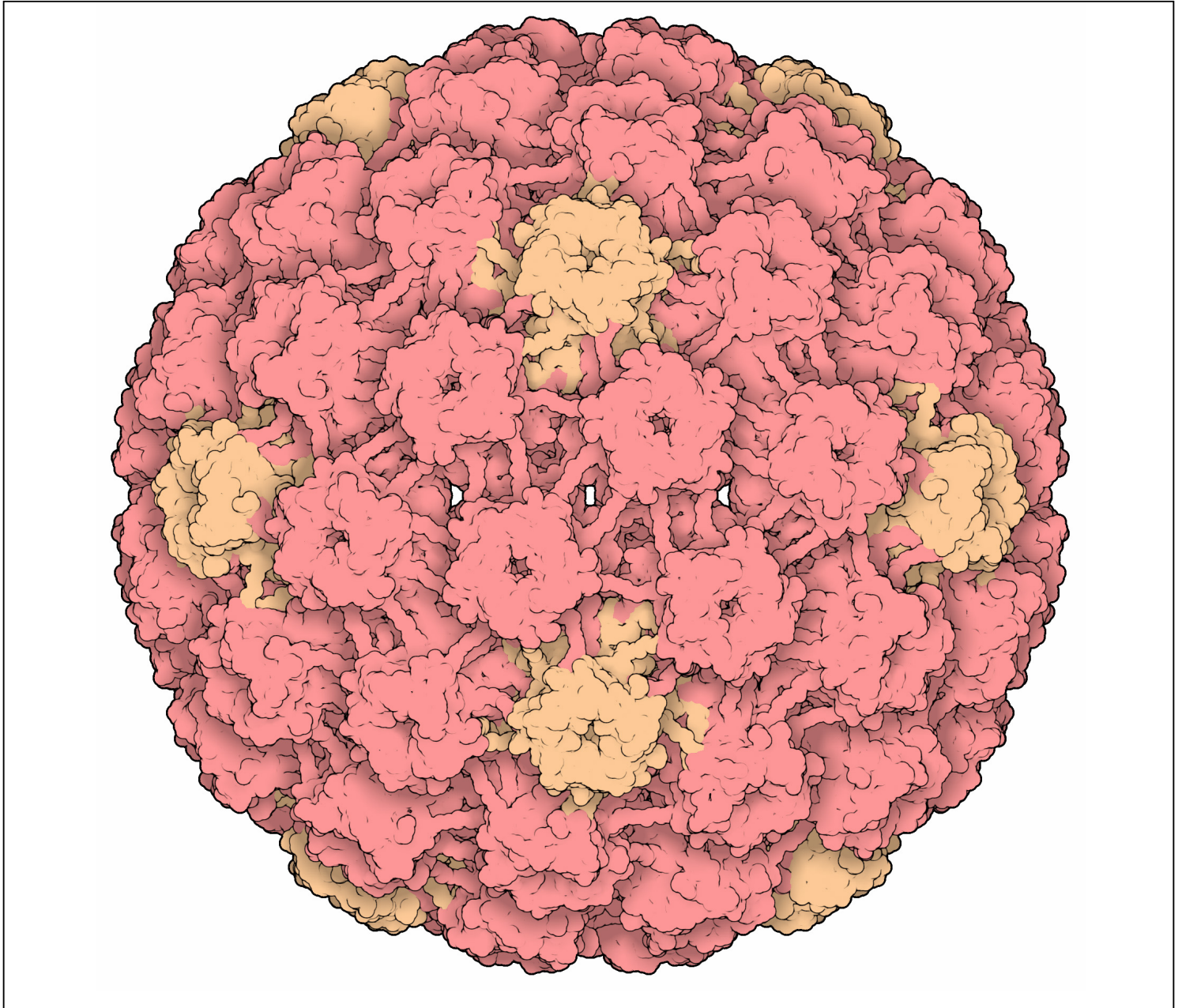
Source: Lewis RM, Laprise JF, Gargano JW, et al. Estimated Prevalence and Incidence of Disease-Associated Human Papillomavirus Types Among 15- to 59-Year-Olds in the United States. Sex Transm Dis. 2021;48:273-7.



### Figure 5 Human papillomavirus (HPV) Capsid

This illustration showing the structures of HPV capsid is based on cryoelectron microscopy. The virus contains 72 pentamers (also referred to as capsomeres), including 12 capsomeres (orange) that are connected with five other capsomeres, and 60 capsomeres (red) that are each connected with six other capsomeres.

Source: Goodsell DS. Human Papillomavirus and Vaccines, Protein Data Bank-101. DOI: 10.2210/rcsb\_pdb/mom\_2018\_5

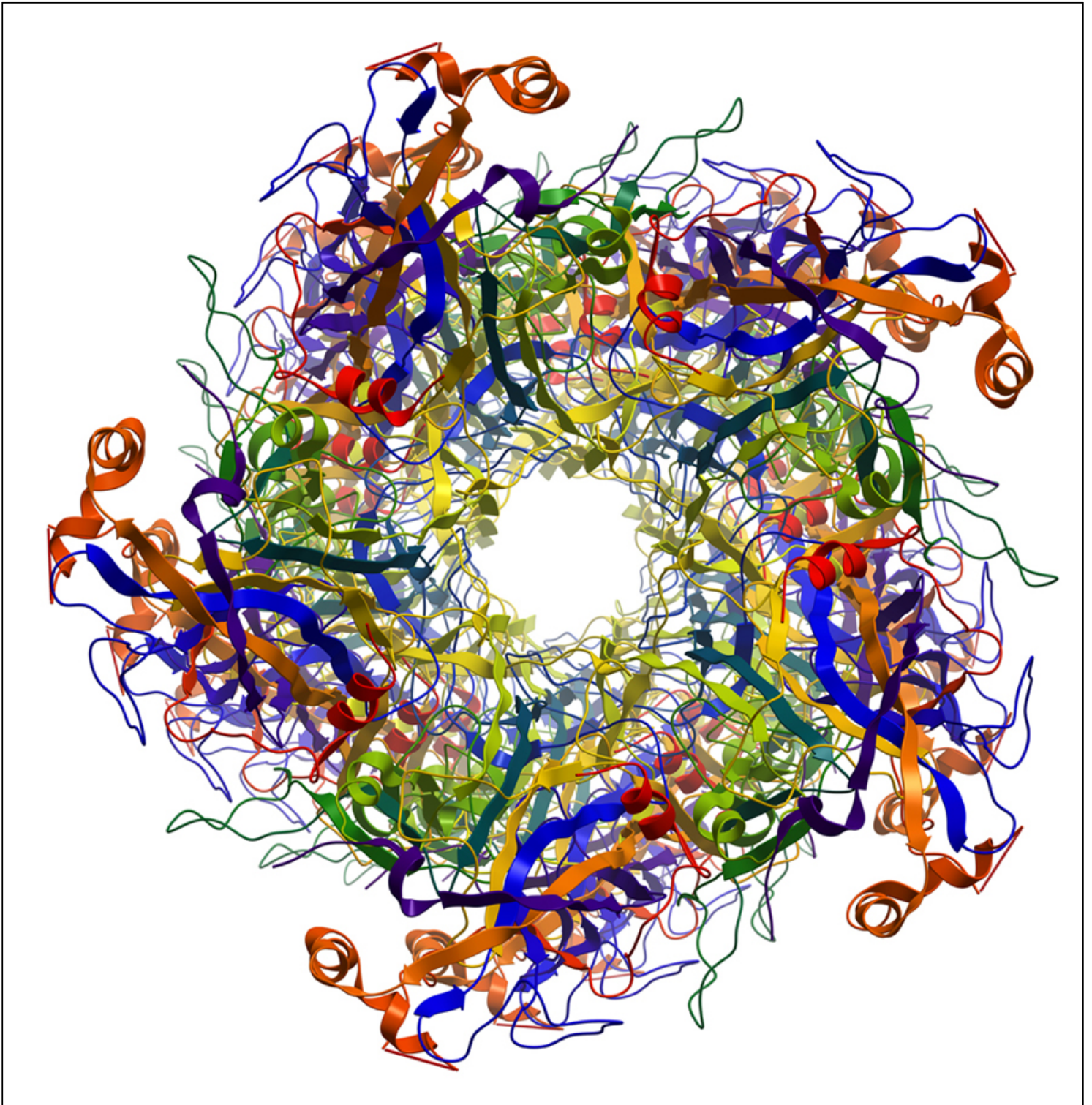




### Figure 6 Human Papillomavirus L1 Pentameric Capsomere

This illustration shows human papillomavirus (HPV) pentameric capsomere which consists of five L1 proteins. Each HPV contains 72 of these pentameric capsomeres.

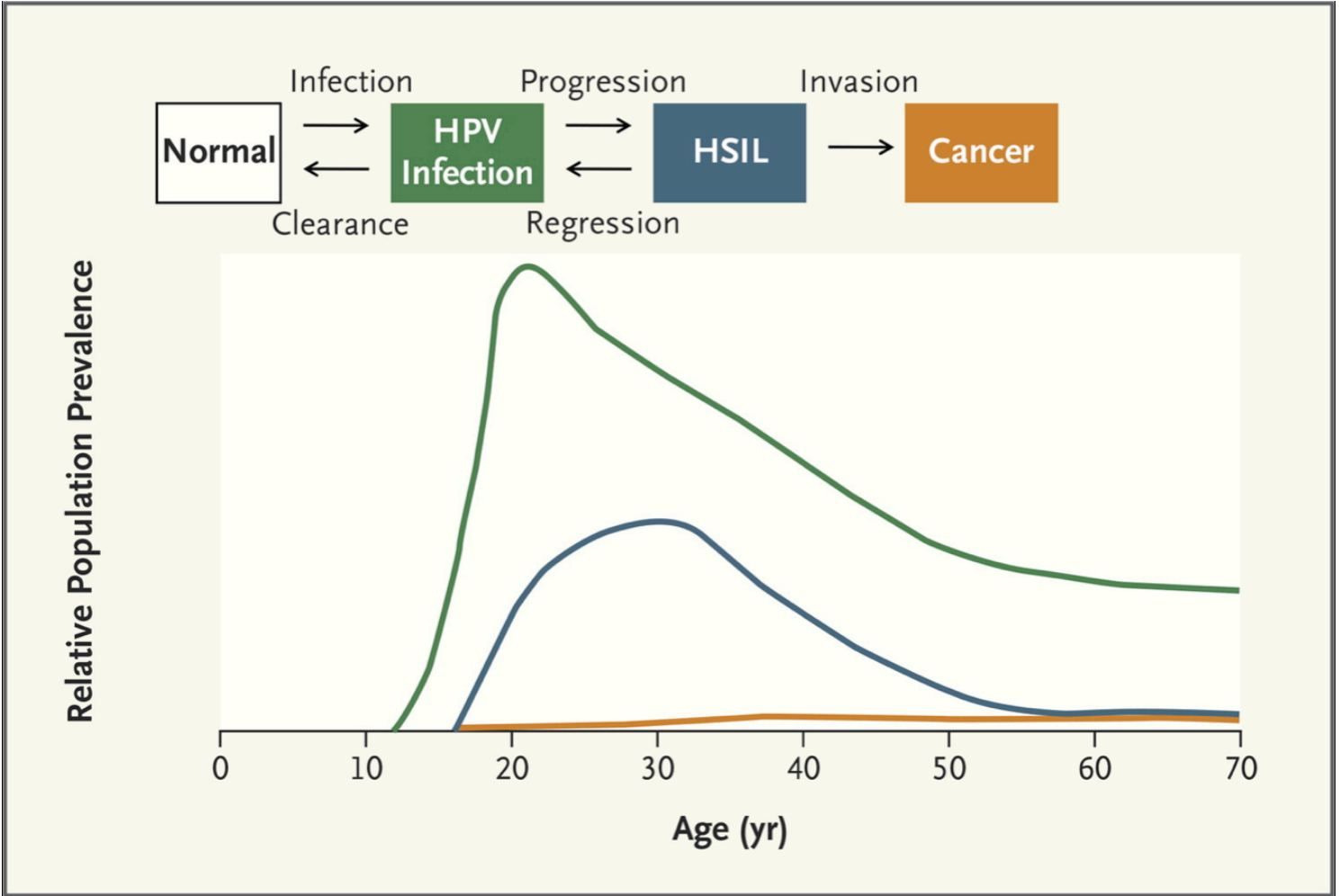
Illustration by Leonid Andropov/Shutterstock.com. Image used under license from Shutterstock.com.



### Figure 7 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.

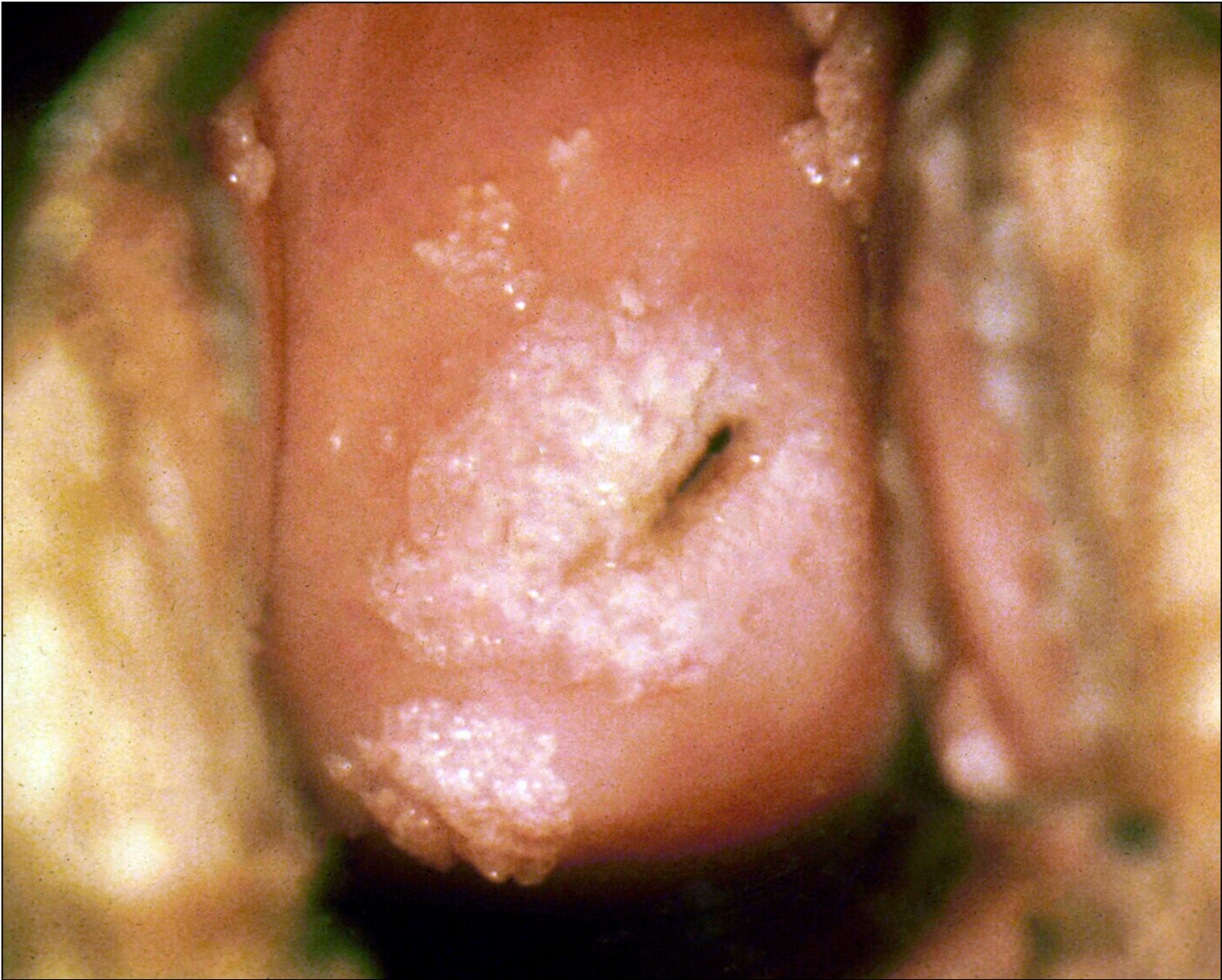
Source: Schiffman M, Solomon D. Clinical practice. Cervical-cancer screening with human papillomavirus and cytologic cotesting. N Engl J Med. 2013;369:2324-31. © 2013 Massachusetts Medical Society. Reproduced with permission.





**Figure 8 Warts on Cervix**

Source: photograph by Claire Stevens, PA Public Health—Seattle & King County Sexual Health Clinic





**Figure 9 Perineal Warts in a Man**

This image shows extensive warts at the base of the scrotum and perianal region.

Source: photograph from Public Health—Seattle & King County Sexual Health Clinic





**Figure 10 Perianal Condylomata**

This image shows extensive perianal condylomas.

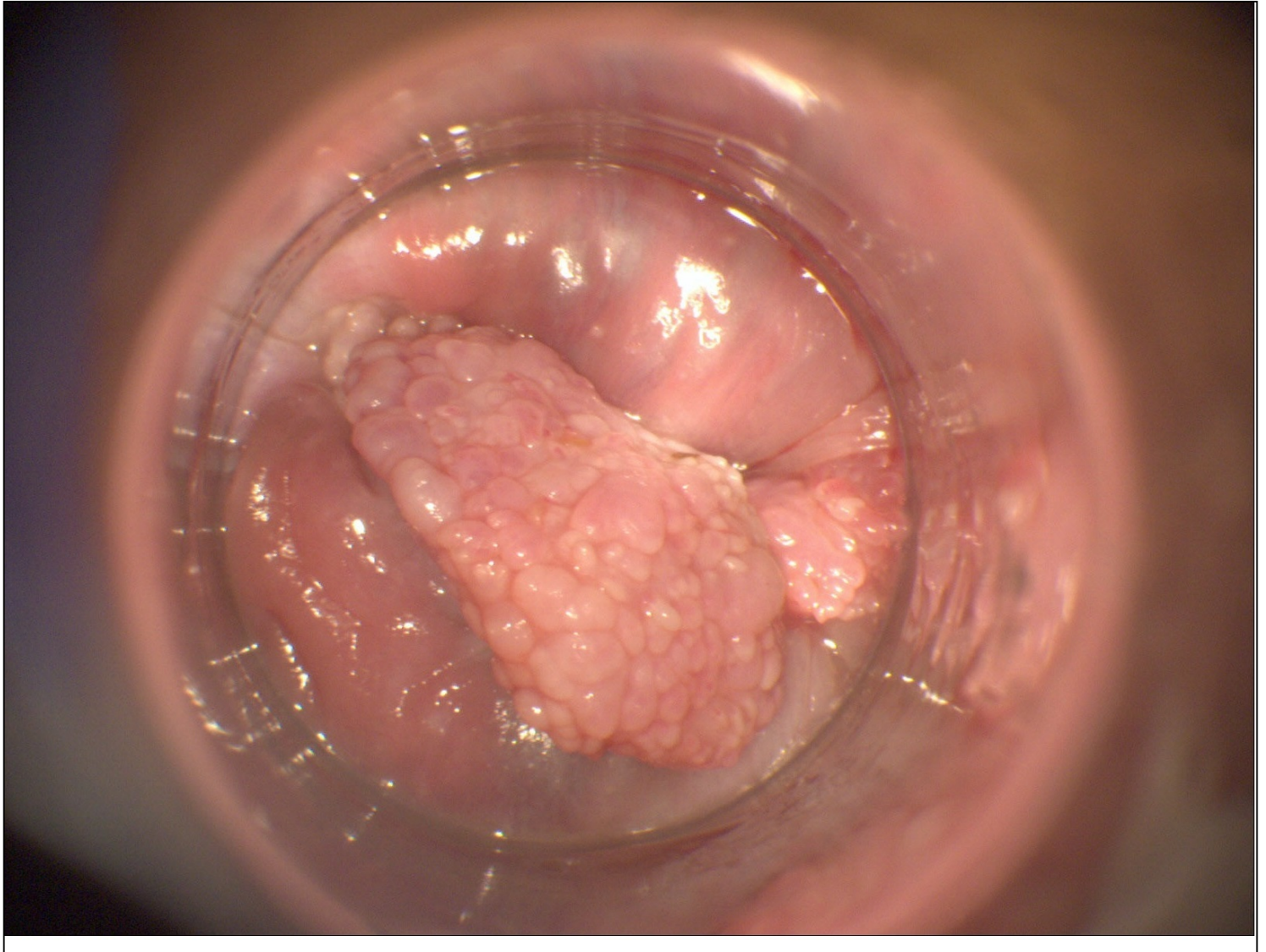
Photograph from Jeffrey T. Schouten, M.D., AAHIVE Departments of Surgery and Medicine Division of Allergy and Infectious Diseases



**Figure 11 Large Intra-Anal Condyloma**

This image shows a large, pedunculated lesion seen in anal canal during anoscopy.

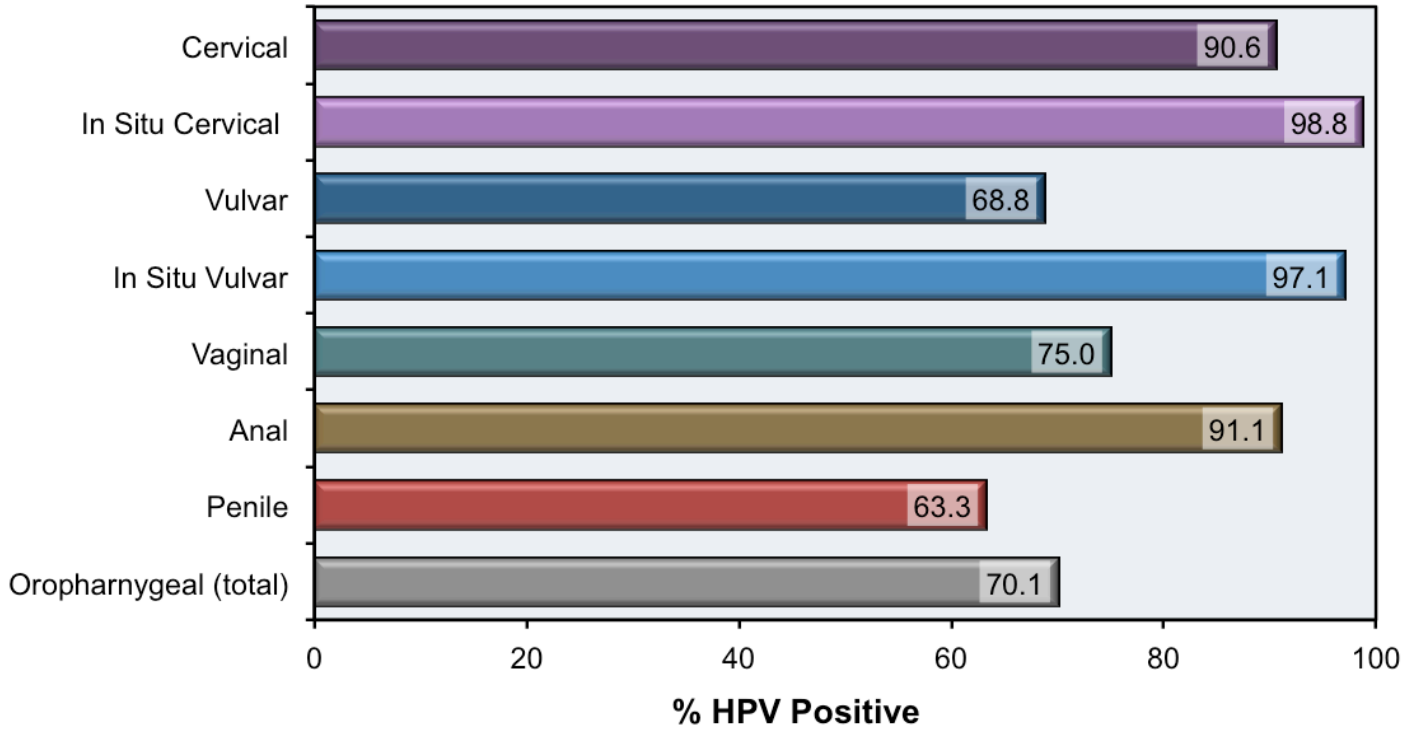
Photograph from Jeffrey T. Schouten, M.D., AAHIVE Departments of Surgery and Medicine Division of Allergy and Infectious Diseases University of Washington



### Figure 12 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 United States population-based cancer registries. The investigators performed HPV testing on samples from 2,670 patients.

Source: Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015;107:djv086.

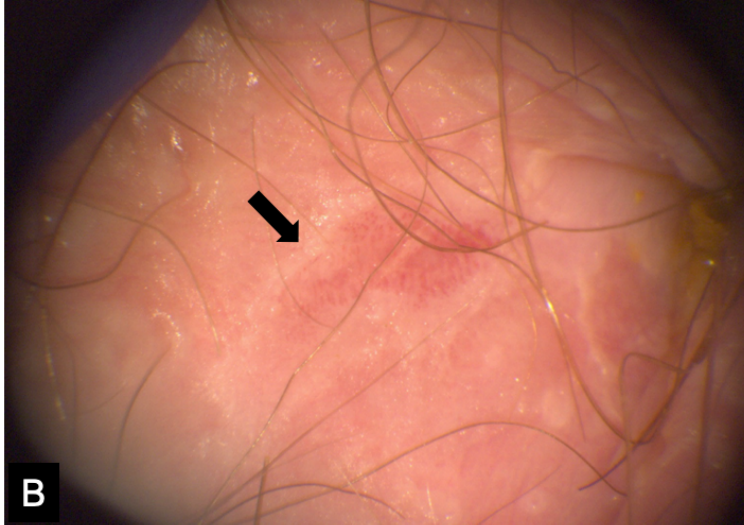
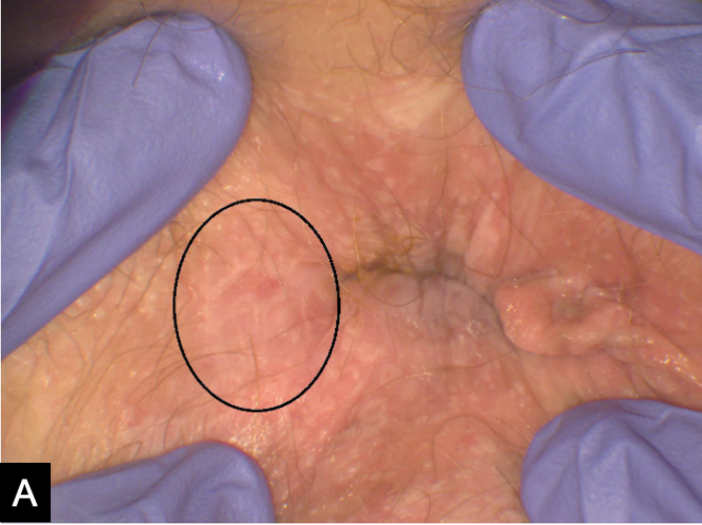




**Figure 13 Perianal High-grade squamous intraepithelial lesion (HSIL)**

Image showing a perianal high-grade squamous intraepithelial lesion (HSIL). Photo A shows small, superficial ulcerative lesion near to the anal verge (black circle). Photo B shows a magnified view of the same lesion using high-resolution anoscopy and acetic acid (black arrow).

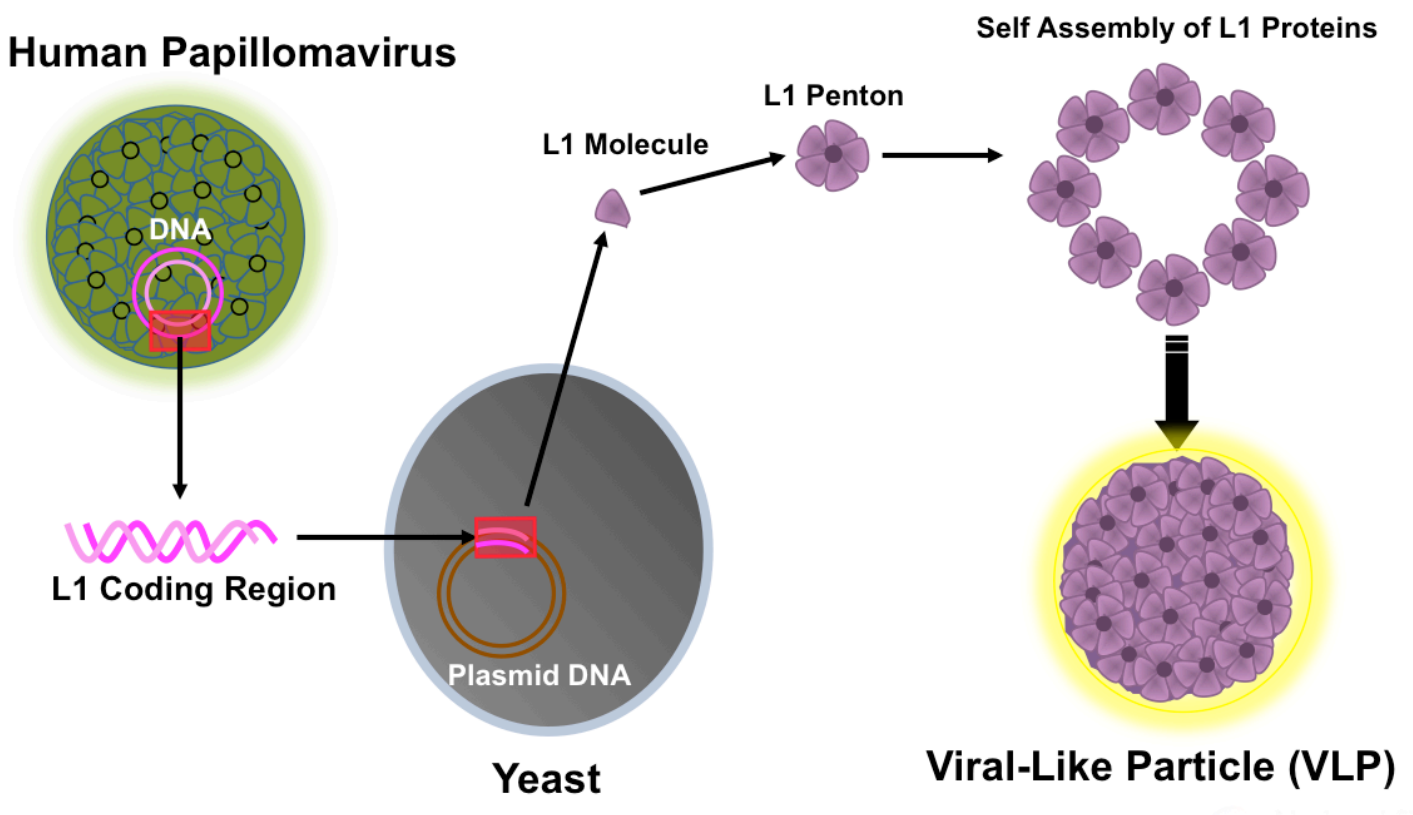
Photographs from Helen Stankiewicz Karita, M.D Division of Allergy and Infectious Diseases University of Washington



### Figure 14 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

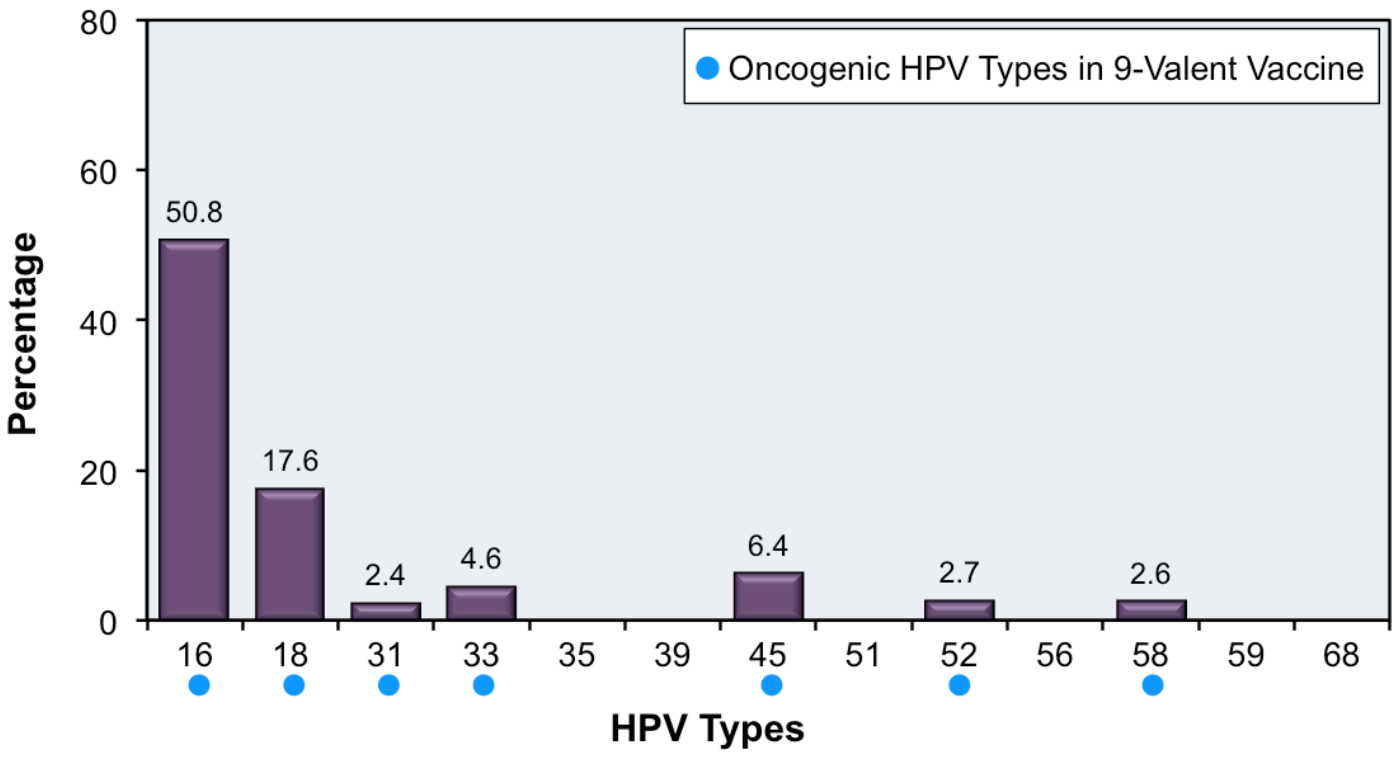


**Figure 15 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine (Image Series) - Figure 15 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine**

**Image 15A: HPV Types and Cervical Cancer**

Source: Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015;107:djv086.

### Cervical Cancer and Oncogenic HPV Types

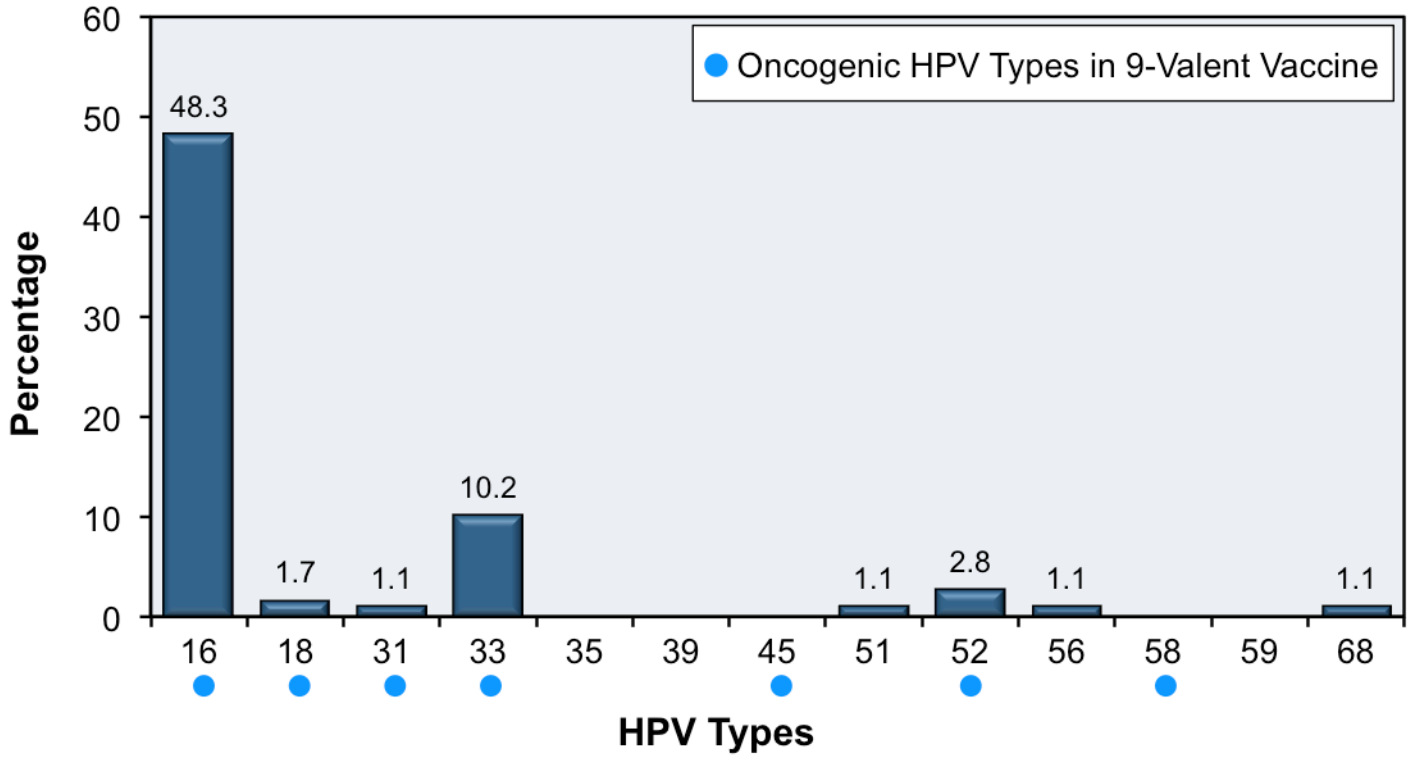


**Figure 15 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine**

**Image 15B: HPV Types and Vulvar Cancer**

Source: Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015;107:djv086.

Vulvar Cancer and Oncogenic HPV Types



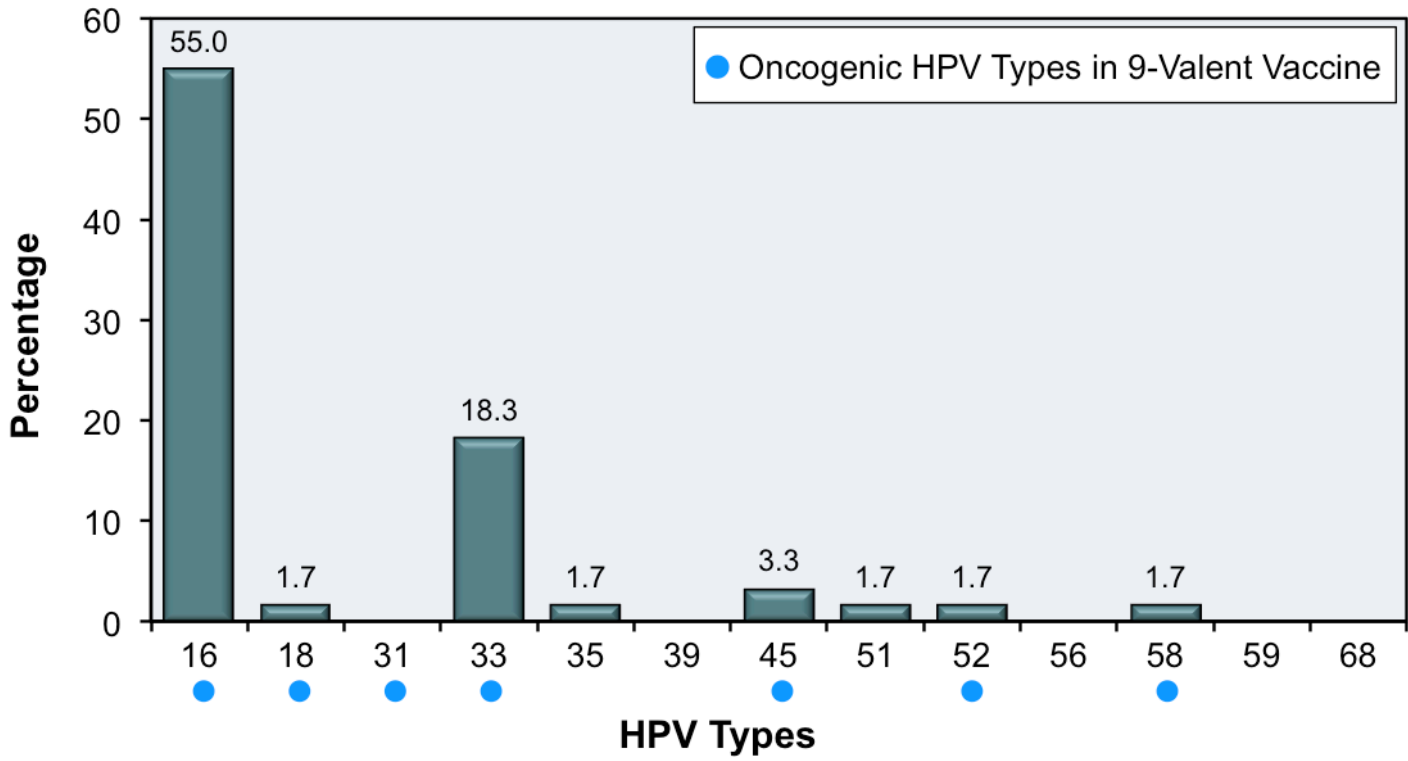


**Figure 15 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine**

**Image 15C: HPV Types and Vaginal Cancer**

Source: Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015;107:djv086.

Vaginal Cancer and Oncogenic HPV Types

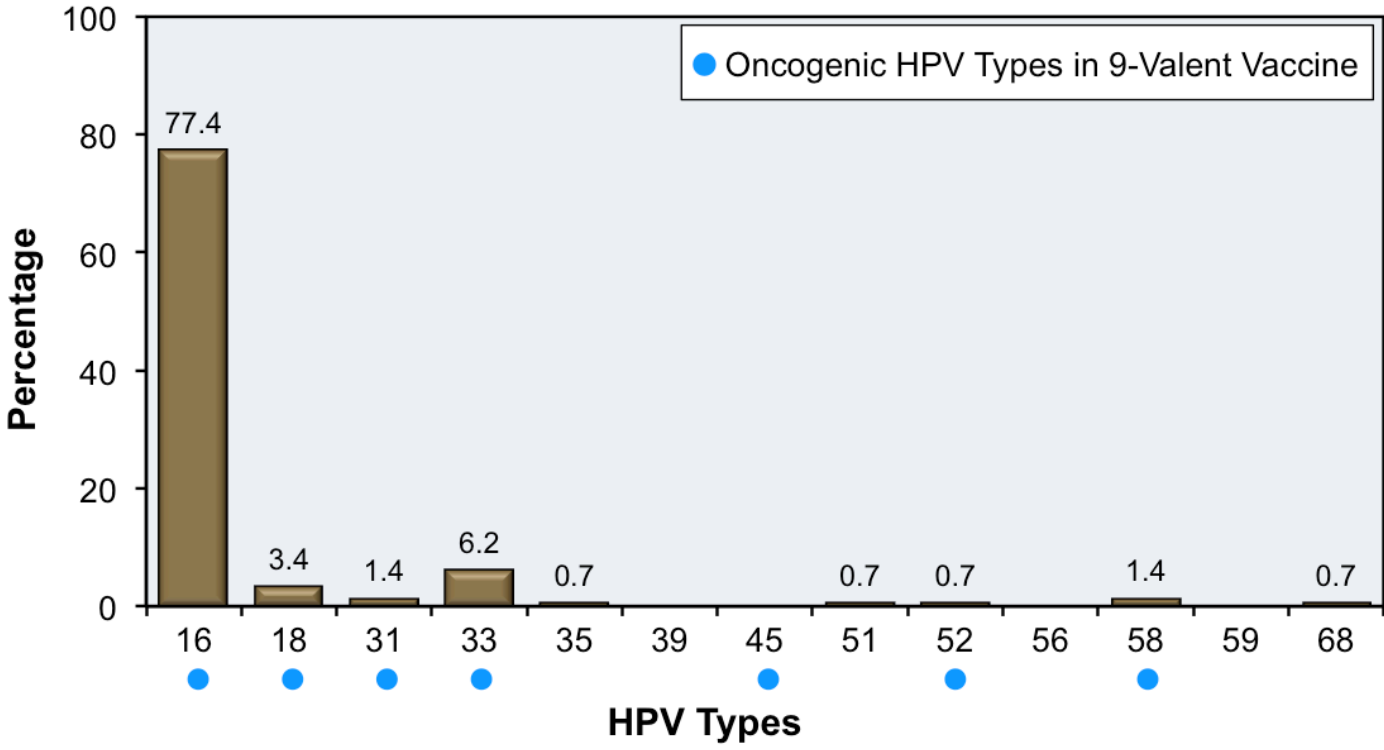


**Figure 15 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine**

**Image 15D: HPV Types and Anal Cancer**

Source: Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015;107:djv086.

**Anal Cancer and Oncogenic HPV Types**

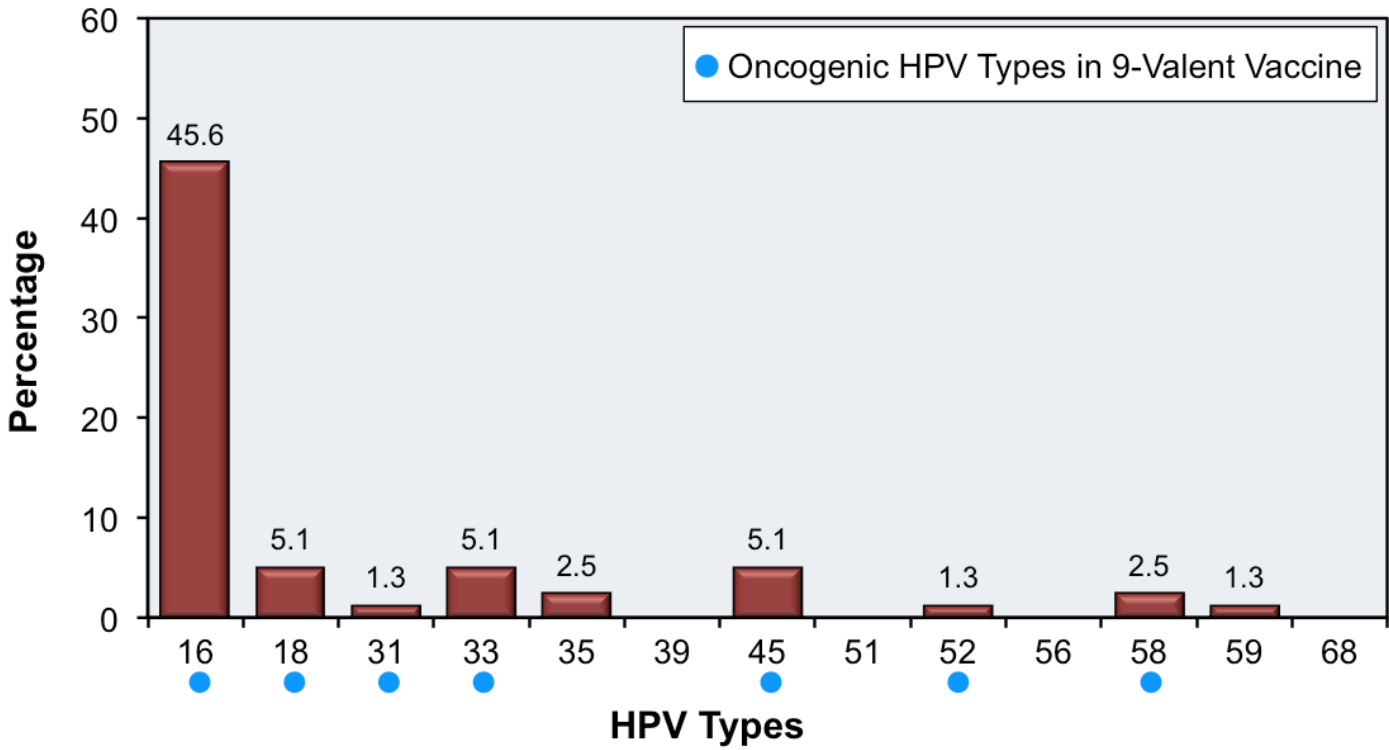


**Figure 15 (Image Series) - HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccine**

**Image 15E: HPV Types and Penile Cancer**

Source: Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015;107:djv086.

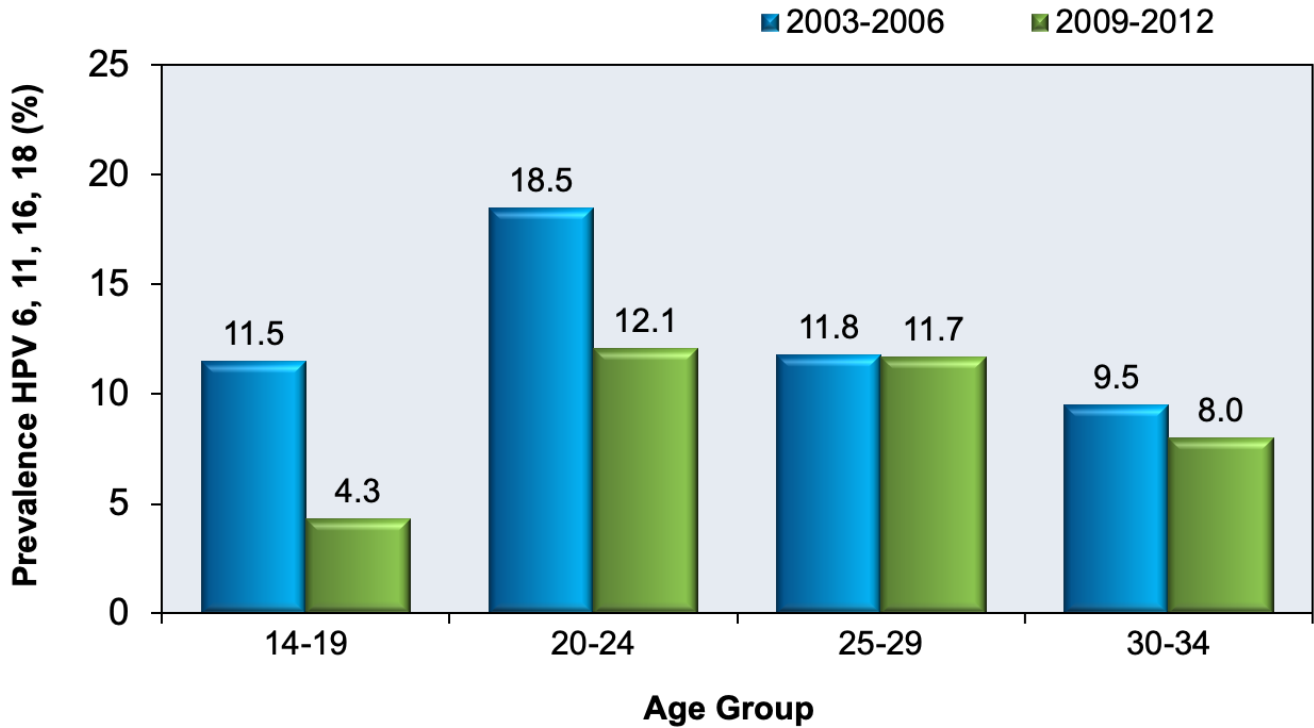
**Penile Cancer and Oncogenic HPV Types**



**Figure 16 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 years, with the prevalence broken out by age group and two time periods: pre-vaccine era (2003-2006) and vaccine era (2009-2012).

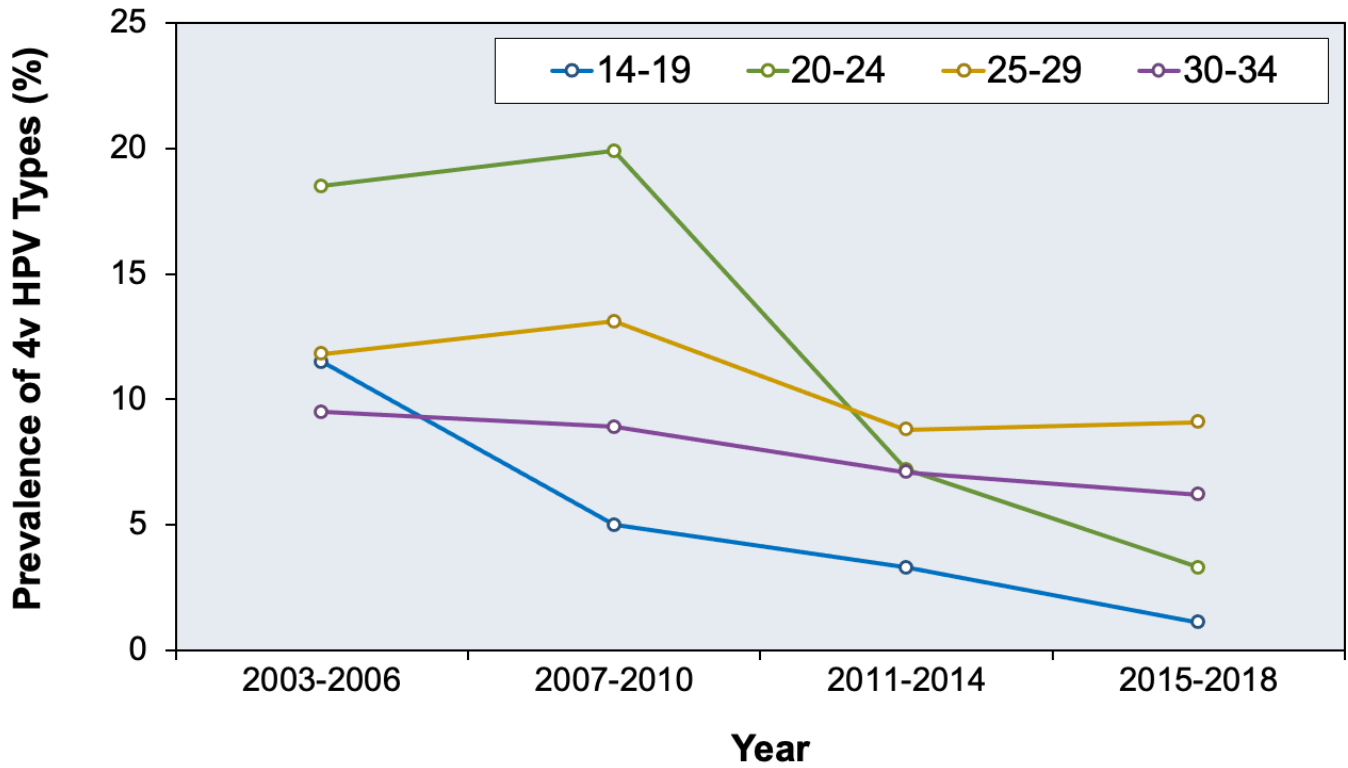
Source: Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV After Introduction of the Vaccination Program in the United States. Pediatrics. 2016;137:e20151968.



**Figure 17 Prevalence of 4vHPV Types among Females Aged 14-34 Years, by Age Group, NHANES, United States**

NHANES = National Health and Nutrition Examination Survey

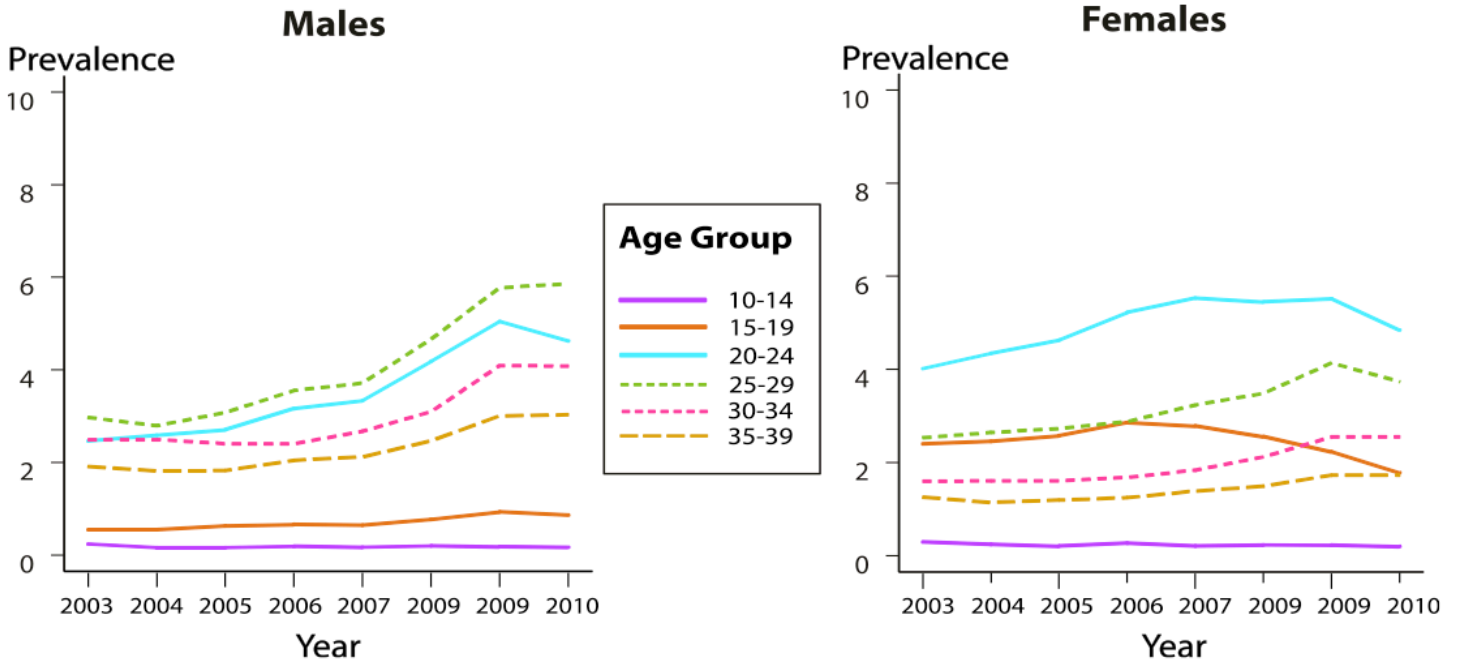
Source: Rosenblum HG, Lewis RM, Gargano JW, Querec TD, Unger ER, Markowitz LE. Declines in Prevalence of Human Papillomavirus Vaccine-Type Infection Among Females after Introduction of Vaccine - United States, 2003-2018. MMWR Morb Mortal Wkly Rep. 2021;70:415-20.



**Figure 18 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 10-39 years of age. These data are from Truven Health Analytics MarketScan Commercial Claims and Encounters Database, United States, 2003-2010.

Source: Flagg EW, Schwartz R, Weinstock H. Prevalence of anogenital warts among participants in private health plans in the United States, 2003-2010: potential impact of human papillomavirus vaccination. *Am J Public Health.* 2013;103:1428-35.



**Figure 19 Trends in Prevalence of Anogenital Warts, U.S. Sexually Transmitted Disease Surveillance Network, 2010-2016**

Source: Mann LM, Llata E, Flagg EW, et al. Trends in the prevalence of anogenital warts among patients at sexually transmitted disease clinics-Sexually Transmitted Disease Surveillance Network, United States, 2010-2016. J Infect Dis. 2019;219:1389-97.

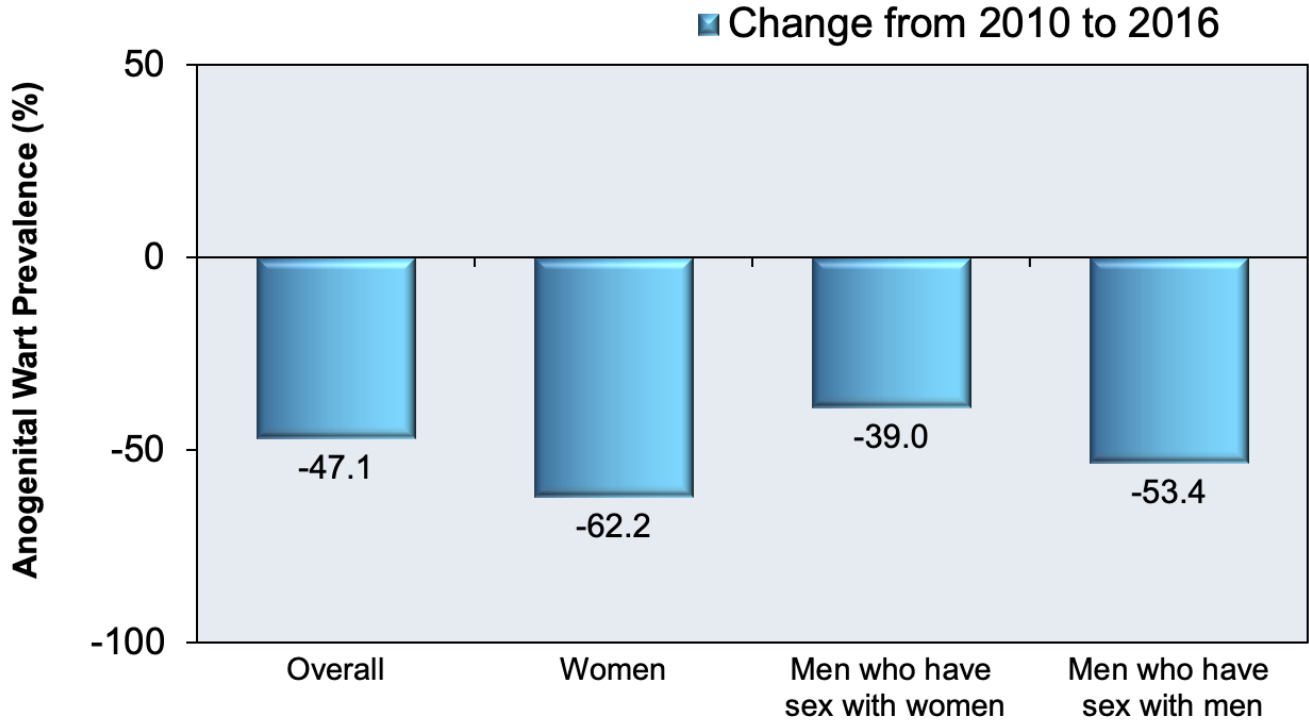




Table 1.

**Human Papillomavirus Types****Low-Risk Types (nononcogenic)**

- Associated with genital warts and benign or low-grade cellular changes (mild Pap test abnormalities).
- Approximately 90% of genital warts are caused by HPV types 6 and 11.
- 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.

**High-Risk Types (oncogenic)**

- 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.
- HPV types 16 and 18 account for approximately 65-70% of cervical cancers.
- The HPV types 31, 33, 45, 52, and 58 cause approximately 10% of all HPV-associated cancers.

Table 2.

**Differential Diagnoses for Anogenital Warts****Manifestations of Other Genital Infections**

- Condylomata lata (manifestation of secondary syphilis)
- Molluscum contagiosum
- Herpes vegetans

**Acquired Dermatologic Conditions**

- Seborrheic keratosis
- Lichen planus
- Fibroepithelial polyp, adenoma
- Melanocytic nevus
- Neoplastic lesions

**Normal Anatomic Variants**

- "Pink pearly penile papules"
- Vestibular papillae (micropapillomatosis labialis)
- Skin tags (acrochordons)

**External Genital Squamous Intraepithelial Lesions (SIL)**

- Squamous cell carcinoma in situ
- Bowenoid papulosis
- Erythroplasia of Queyrat
- Bowen's diseases of the genitalia

### Table 3. 2021 STI Treatment Guidelines: Anogenital Warts Treatment of External Anogenital Warts

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

#### Recommended for PATIENT-APPLIED Therapy

##### Imiquimod 3.75% cream

*Apply the 3.75% cream once at bedtime, every night consecutively for up to 8 weeks.*

The treatment area should be washed with soap and water 6-10 hours after the application.

Note: The imiquimod cream might weaken condoms and vaginal diaphragms.

#### Recommended for PATIENT-APPLIED Therapy

##### Imiquimod 5% cream

*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.

Note: The imiquimod cream might weaken condoms and vaginal diaphragms.

#### Recommended for PATIENT-APPLIED Therapy

##### Podofilox 0.5% solution or gel

*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.*

The total wart area treated should not exceed 10 cm<sup>2</sup>, and the total volume of podofilox should be limited to 0.5 mL per day.

#### Recommended for PATIENT-APPLIED Therapy

##### Sinecatechins 15% ointment

*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.

Note: Sinecatechins might weaken condoms and vaginal diaphragms.

#### Recommended for PROVIDER-ADMINISTERED Therapy

##### Cryotherapy with liquid nitrogen or cryoprobe

*Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large.*

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

#### Recommended for PROVIDER-ADMINISTERED Therapy

##### Surgical removal either by tangential scissor excision, tangential shave

*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 (CO<sub>2</sub>) laser, or by curettage.*

Note: 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 Dichloroacetic acid (DCA) 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 or DCA treatment can be repeated weekly if necessary.

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

\*Persons with external anal or perianal warts might 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.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Human papillomavirus (HPV) infection: anogenital warts. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [[2021 STI Treatment Guidelines](#)]

**Table 4. 2021 STI Treatment Guidelines: Anogenital Warts  
Treatment of Internal Anogenital Warts**

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

**Recommended for Urethral Meatus Warts**

**Cryotherapy with liquid nitrogen**

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 Urethral Meatus Warts**

**Surgical removal**

**Recommended for Vaginal Warts**

**Cryotherapy with liquid nitrogen**

Note: The use of a cryoprobe in the vagina is NOT recommended because of the risk for vaginal perforation and fistula formation.

**Recommended for Vaginal Warts**

**Surgical removal**

**Recommended for Vaginal Warts**

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

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

**Recommended for Cervical Warts**

**Cryotherapy with liquid nitrogen**

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.

**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.

**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.

**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.

Source: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Human papillomavirus (HPV) infection: anogenital warts. MMWR Recomm Rep. 2021;70(No. RR-4):1-187. [[2021 STI Treatment Guidelines](#)]

