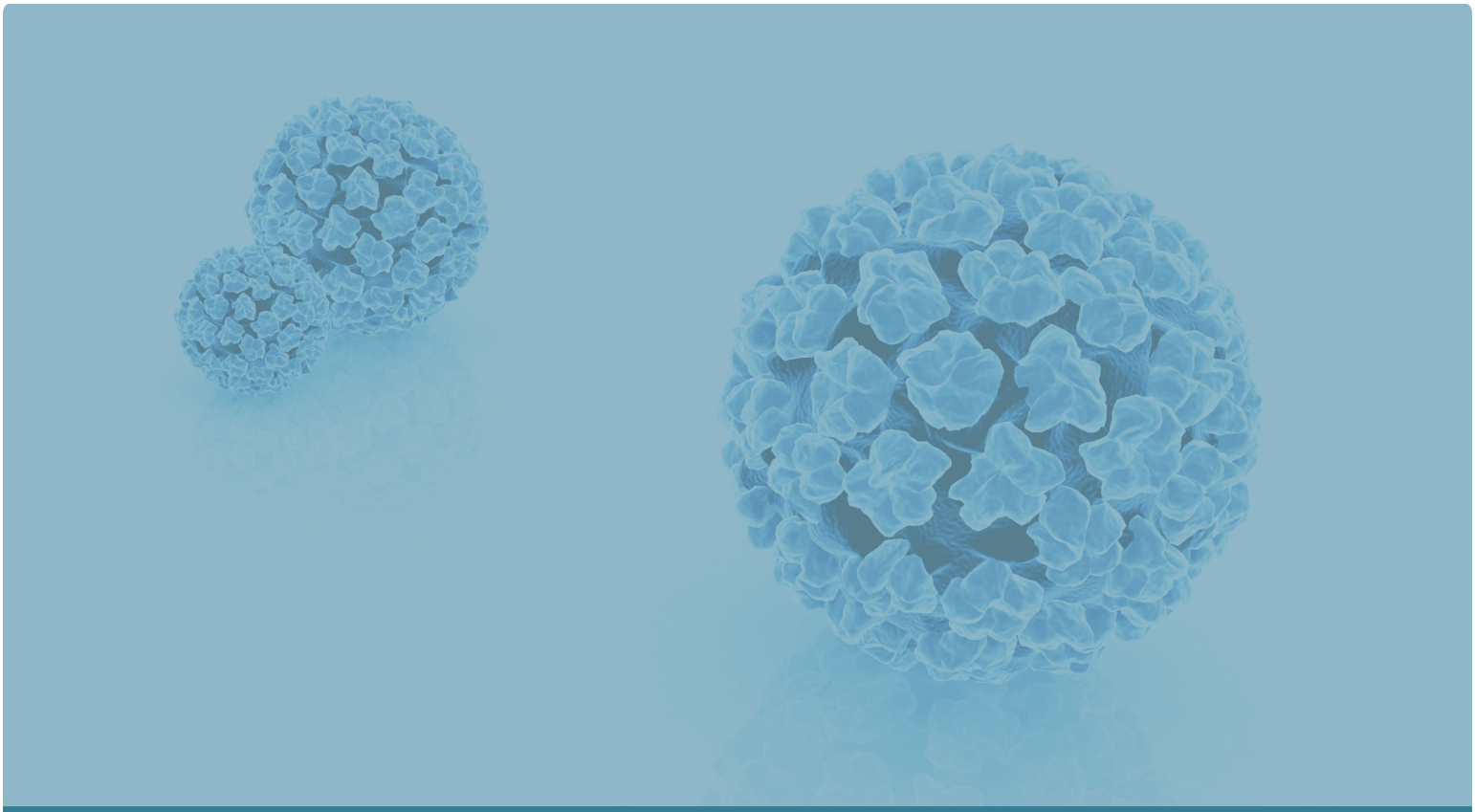


THE HPV TOOLKIT

A Resource For Healthcare Providers

asha
American Sexual Health Association

INTRODUCTION

Anogenital human papillomavirus (HPV) infections are nearly ubiquitous among sexually active individuals: data indicate that up to 80% of sexually active persons experience one or more anogenital HPV infections.[1] The incidence of anogenital HPV infection in the United States is estimated to exceed 14 million cases per year.[2]

Persistent infection of oncogenic HPV types is the cause of squamous cell cancers of the cervix, penis, vagina, vulva, and anus, as well as other squamous intraepithelial lesions (SILs) that often are precursors to cancer.[3] There is also a link between one oncogenic HPV genotype, HPV16, and a subset of squamous cell carcinomas of the oropharynx.[4]

Nononcogenic ("low-risk" types) rarely cause cancer, but 2 low-risk types—HPV6 and 11—cause approximately 90% of genital warts.[5] Occasionally, the same types cause oral and laryngeal warts and, rarely, recurrent respiratory papillomatosis.

The last 15 years have brought new screening technologies, vaccines, treatment options, and updated guidelines that have revolutionized the diagnosis and management of patients with sexually transmitted HPV and related diseases, especially with regard to cervical cancer screening and HPV vaccines.

CERVICAL CANCER SCREENING

Widely available Pap testing in the United States has led to tremendous reductions in the incidence and mortality of cervical cancer.[6] Once the leading cause of cancer death among women in the United States, annual mortality per 100,000 women decreased from 5.55 in 1975 to 2.3 in 2012. In the same interval, incidence dropped from 14.79 cases per 100,000 women to 5.6.[7]

HPV TESTS

A significant change to cervical cancer screening technology occurred in the 1990s with licensure of the first HPV DNA test to detect oncogenic types of the virus in clinical settings. Testing for high-risk HPV is useful as a tool to triage patients who are at greater risk for cervical precancers/cancer and are likely to benefit from colposcopy.[8] Several such tests are now on the market in the United States and, in conjunction with cervical cytology, are approved for use in specific screening situations:

1. As a follow-up test if the Pap result is unclear or borderline abnormal, as when atypical squamous cells of undetermined significance (ASC-US) are observed.[8]

2. As a routine cervical cancer screening test in combination with a Pap test in women at or over 30 years of age (rather than just having the Pap test alone). Most anogenital HPV infections are acquired from the teen years through age 26; most infections resolve spontaneously, and most cancers result from long-persisting high-risk HPV infection.[9,10] Therefore, HPV infections in women over 30 years of age are more likely to be a persistent infection and more likely to be associated with premalignant neoplasia or cancer, whereas most infections in younger women are transient and less likely to progress.[11] Thus, the combination test (Pap test plus HPV testing) can increase the effectiveness of detecting any problems early on, especially in women ≥30 years of age.[8]

Additionally, HPV16/18 genotyping tests have been available since 2009. These tests check directly for HPV types 16 and 18, which together are responsible for approximately 70% of cervical cancers.[12] The potential advantage to genotyping may be to allow women who are high-risk HPV-positive, but negative for the more aggressive HPV16/18 types, to avoid immediate referral to colposcopy in favor of repeating Pap and HPV tests in 12 months.[13]

In 2014 the FDA approved the **first HPV test to be used as primary screening for cervical cancer**, which allows testing for HPV without cervical cytology as a co-test. This test, approved for use with women aged 25 and older, detects 14 oncogenic genotypes while also detecting HPV 16/18 specifically. Several professional organizations collaborated and published interim guidance on the use of HPV primary testing and these recommendations are summarized in the next section.

CERVICAL CANCER SCREENING GUIDELINES

In 2012 updated cervical cancer screening guidelines were issued by the both the USPSTF and the Cervical Cancer Guideline Committee of the ACS-ASCCP-ASCP. The two sets of guidelines were developed separately but are in agreement in most respects. Major changes include delaying the onset of cervical cancer screening to age 21 regardless of sexual history and lengthening of screening intervals to 3-5 years. A summary of both guidelines is below:[14,15]

- **Cervical cancer screening should begin at age 21.**
  Most HPV infections acquired in teens and young adults clear up spontaneously, including those caused by high-risk types.[16] It is now recognized that screening young women soon after onset of sexual activity results in large numbers of HPV infections and Pap test abnormalities that can safely be ignored, but that historically have resulted in unnecessary treatment accompanied by preventable anxiety and stress.
- **For women ages 20-29, screening with cytology alone every three years**
- **For women 30 and over:**
  - Screening every five years with cytology/HPV testing (ACS guidelines say "co-testing" is the preferred approach)
    OR
  - Screening every three years with cytology alone
- **For women 65 and over:**
  Cervical cancer screening can end for most women at age 65, provided they have a history of adequate screening tests with normal results
- **Post-hysterectomy:**
  Screening is not recommended for women of any age after removal of the cervix unless there is a history of significant cervical precancer (CIN2 or higher).

Representatives from professional organizations working in gynecology, oncology, and pathology collaborated to publish interim guidance on the best use of HPV primary testing to screen for cervical cancer. The resulting algorithm calls for referral to cervical cytology for patients positive for an oncogenic HPV genotype; those positive for HPV 16/18 should be referred for immediate colposcopy. Rescreening intervals for those with negative HPV primary tests should not occur more frequently than every three years.[17]

Note: some women and healthcare provider alike have expressed concern over the extended screening intervals, which is not surprising given the traditional "annual Pap" mindset. Evidence shows that screening intervals can indeed be safely lengthened and doing so will likely result in reduced morbidity associated with over-screening (such as unnecessary referrals to colposcopy).[14]

HPV VACCINES

BACKGROUND

The past decade has seen the development of 3 vaccines to prevent HPV infection.

- In 2006, a quadrivalent HPV vaccine (Gardasil®) was approved by the Food and Drug Administration (FDA) for use in the United States, followed in 2009 with the approval of a bivalent vaccine (Cervarix®). Both are nearly 100% protective against HPV 16 and 18, which together cause about 70% of cervical cancers.[2]
- The quadrivalent vaccine also is approximately 100% effective in preventing infection with HPV 6 and 11, which together are responsible for nearly all instances of genital warts.[2]
- In 2014, Gardasil®9 became available in the U.S. In addition to protecting against the HPV types covered in the quadravalent version of Gardasil®, the 9-valent vaccine also protects against five additional oncogenic types (31, 33, 45, 52, and 58). The oncogenic HPV types covered by Gardasil®9 are detected in about 80%-90% of all cervical cancers.[5]

HPV VACCINE INDICATIONS

The **quadrivalent vaccine** is approved by the Food and Drug Administration (FDA) for use in the United States in:[18]

- Girls and young women aged 9 to 26 years for the prevention of cervical, vulvar, and vaginal cancers and precancers caused by HPV types 16 and 18.
- Males and females aged 9 to 26 years to prevent genital warts (condyloma acuminata) associated with HPV types 6 and 11.
- Males and females aged 9 to 26 years to prevent anal cancers, precancers, and dysplasia caused by HPV types 6, 11, 16, and 18.

The **bivalent vaccine** is approved by the FDA for use in the United States in:[19]

- Females aged 10 to 25 years for the prevention of cervical cancers and precancers associated with HPV 16 and HPV 18.

The **nine-valent vaccine** is approved by the FDA for use in the United States in:[20]

- Females aged 9-26 to prevent cervical, vaginal, vulvar, anal cancers and precancers associated with HPV types 16, 18, 31, 33, 45, 52, and 58.
- Females aged 9-26 to prevent genital warts associated with HPV types 6 and 11.
- Males aged 9-26 to prevent genital warts associated with HPV types 6 and 11 and anal cancers and precancers associated with HPV types 16, 18, 31, 33, 45, 52, and 58.

The emphasis on preteen and teenage groups is intended to maximize protection, because many HPV infections are acquired soon after onset of sexual activity.[9]

HPV VACCINATION RECOMMENDATIONS

Females may receive the bivalent, quadrivalent, or nine-valent vaccine. Males may receive the quadrivalent or nine-valent vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP) for use of HPV vaccines in males and females.[5]

- Routine vaccination at age 11 or 12 years for all males and females
- Vaccination for females aged 13-26 and males aged 13-21 who have not been vaccinated (or who didn't receive all three doses)
- Vaccination is also recommended through age 26 for men who have sex with men and those who are immunocompromised

Dosing schedules with the vaccines are at 0, 1 to 2 months, and 6 months. Minimum intervals are 4 weeks between doses 1 and 2, 12 weeks between doses 2 and 3, and 24 weeks between the first and third doses. It is likely that variations in scheduled doses do not seriously impair the vaccines' effectiveness; therefore, the vaccine series should not be restarted if the schedule is interrupted.

SAFETY AND SIDE EFFECTS

In studies with tens of thousands of males and females worldwide, HPV vaccines have been shown to be effective, safe, and well tolerated. Adverse events (AEs) are no greater in those receiving an HPV vaccine than background rates of other vaccines for this age group. There is no difference between vaccine and control groups in serious AEs, new onset chronic disease and autoimmune disorders, or deaths.[2]

The most common local symptoms reported are pain, swelling, and redness at the injection site. The most common general symptoms include headache, nausea, and fever.[2] To avoid syncope (fainting), patients should sit or lie down for 15 minutes after the vaccine has been administered and before leaving the office or clinic.[2]

Contraindications include:[2]

- Pregnancy
- Those with a severe allergic reaction (e.g., anaphylaxis) after previous dose
- With the quadrivalent vaccine, a history of immediate hypersensitivity to yeast
- Prefilled syringes of the bivalent vaccine are contraindicated for those with anaphylactic latex allergy (single-dose vials of the bivalent vaccine have no latex)

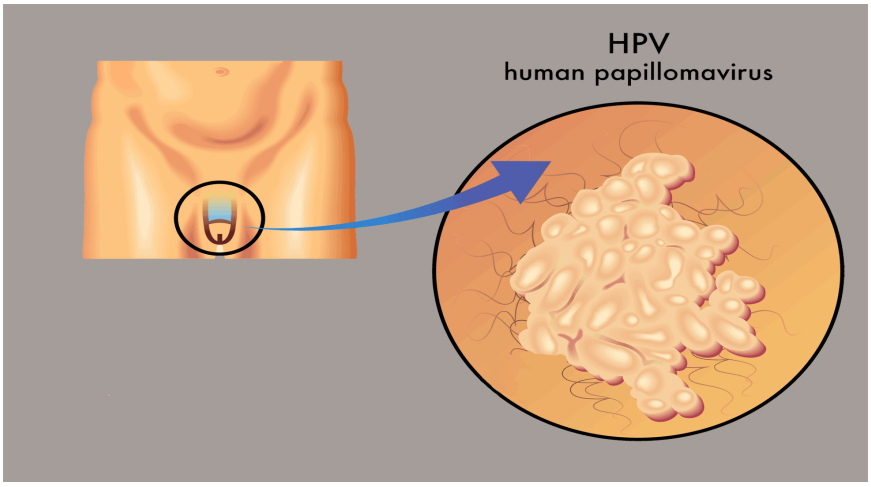
GENITAL WARTS

Approximately 360,000 individuals develop anogenital warts in the U.S. each year.[16] Overall, it has been estimated that 6% of US residents report a history of genital warts.[1] Warts vary in appearance: most lesions are external and can be raised (i.e.,"cauliflower" formation) or flat, single or multiple, small or large. Typically, warts are asymptomatic but sometimes itch, bleed, or cause irritation.[1] Warts can be found in multiple anogenital sites including the vulva, vagina, cervix (less common), penis (including under the foreskin in uncircumcised ales), scrotum, urethra, anus, and perineum.[21] The groin and lower abdomen can be involved, but this is uncommon.

Visual inspection by an experienced clinician usually is sufficient for accurate diagnosis. However, biopsy sometimes is required if the visual diagnosis is uncertain or for lesions that are uncharacteristic in appearance (e.g., pigmented or ulcerated).[21] The currently available HPV tests are not approved or recommended for diagnosis of warts.

TREATMENT OF GENITAL WARTS

The goal of treatment is to eliminate warts. While it is possible that doing so helps prevent transmission by reducing the HPV viral load, this is speculative. No available therapy has been shown to cure HPV infection or reduce the risk of transmission, in part because the virus typically is also present in skin or mucosa that appears normal, without visible warts.



There are numerous therapeutic options for genital warts, including both provider- and patient-directed treatments. No single approach to treating warts is universally superior. The selection of a treatment option is influenced by factors that include size of warts, anatomic site, number and distribution of lesions, as well as provider and patient preferences.[21] Warts eventually regress naturally, sometimes within a few months, so a "watchful waiting" approach occasionally is appropriate. Recurrences are not uncommon, especially in the first 3 months following therapy. With the exception of surgery or other forms of direct destruction or removal, all recommended treatments are only 60% to 80% effective in ablating warts, and none are more effective than others in preventing recurrence.[1] When a particular treatment is not effective or if warts regrow within 3 months, a different modality should be used. Some experts routinely use combination therapy, such as initial cryotherapy followed by a patient-applied treatment.

Treatment regimens for genital warts are outlined below. Information is summarized from the Centers for Disease Control and Prevention (CDC) 2015 STD treatment guidelines, except where noted.[21]

PATIENT-APPLIED PRESCRIPTION TREATMENTS

- **Podofilox (Condylox®):** Podofilox is a purified derivative of podophyllin resin, and is available as a topical solution or gel.23 Podofilox is applied to genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated up to 4 times. Podofilox use is contraindicated during pregnancy.

- **Imiquimod (3.75% cream or 5% cream)**: Imiquimod is a topical immune response modifier. Imiquimod 3.75% cream one daily at bedtime for up to 16 weeks.[23] Imiquimod 5% cream can be used 3 times a week (i.e., every other night before bed) for up to 16 weeks. Patients should wash their hands after applying imiquimod, and the cream should be washed off approximately 8 hours after application.[23] Imiquimod is substantially less effective against warts on dry surfaces than those on moist surfaces (e.g., the vulva or under the foreskin). Imiquimod has not been studied in pregnant women.[23]

- **Sinecatechins 15% ointment**: This extract is developed from green tea. Available as an ointment, sinecatechins is applied to warts 3 times daily for as long as 16 weeks. Side effects include local irritation including rashes, itching, burning, and ulceration. Sinecatechins is contraindicated during pregnancy.

PROVIDER-APPLIED TREATMENTS

- **Trichloroacetic acid (TCA) and bichloroacetic acid (BCA)**: Highly caustic acid compounds that are quite effective in rapidly ablating warts, but occasionally cause short but intense pain.[1] Care must be taken to prevent contact with normal skin, and some providers protect the area around warts with petroleum jelly.[24] Treatment can be repeated weekly, if necessary. Safe to use during pregnancy.[22]

- **Cryotherapy**: Freezing tissue (usually liquid nitrogen), which directly destroys wart tissue by thermal injury. After treatment, the outer layer of tissue forms a blister and separates from deeper layers. Cryotherapy is very efficacious but painful local reactions (e.g.,blistering and pain) are common.[24]

- **Surgery and related methods**: For appropriately trained clinicians, direct surgical removal may be appropriate, especially for certain locations (e.g., intraurethral warts) or particularly large warts. Other related methods also requiring sophisticated training include laser therapy and electrocautery.

HPV-RELATED CANCERS

ANAL CANCER

Most anal cancers are squamous cell carcinomas occurring in the anorectal junction (a squamocolumnar transition area similar to that of the cervix).[25,26] Estimated incidence and mortality in the U.S. is 7,200 and 1000, respectively; populations at highest include men-who-have-sex-with-men (MSM) and HIV-positive individuals.[27]

Not all cases are symptomatic. Signs and symptoms, when present, include:

- Bleeding, itching, discharge, or pain with the anus or rectum (symptoms can mimic those found with hemorrhoids)
- Masses or bumps in the anus
- Swollen glands in the groin or anus
- Change in stools or bowel movements

While there are no consensus guidelines on screening, some experts recommend screening at-risk populations -including MSM and all HIV-positive individuals- with anal cytology.[26] Patients with abnormalities detected are referred to high-resolution anoscopy (HRA), a diagnostic procedure analogous to cervical colposcopy.[26]

VULVAR CANCER

Most vulvar cancers (approximately 90%) are squamous cell carcinomas. Other vulvar cancers include adenocarcinomas (that develop in the Bartholin's glands) and melanoma (most often occurring on the labia minora or clitoris).[29] Vulvar cancer incidence and mortality in the U.S. is estimated at 5,150 and 1,080, respectively.[30] About half of vulvar cancers are associated with oncogenic HPV.[31]

Risk Factors:[29]

- Increasing age. The risk of vulvar cancer increases with age, though it can occur at any age. The average age at diagnosis is 65.
- Oncogenic HPV infection
- Smoking
- Being infected with HIV
- Having a history of precancerous conditions of the vulva
- Having a skin condition involving the vulva

Vulvar precancers (Vulvar intraepithelial neoplasia or VIN) are often asymptomatic, although some patients experience elevated lesions (flat lesions can occur, too) that may be lighter or darker than the surrounding skin.[32] Symptoms of invasive vulvar cancer may be similar to the precursor lesions: persistent itching, skin areas that are reddish/pink or darkened, condyloma-like lesions, dysuria, and vulvar tenderness or pain.[30]

VAGINAL CANCER

80%-90% of vaginal cancers are squamous cell carcinomas, the vast majority of which are related to oncogenic HPV. Incidence and mortality in the U.S. is estimated at 4,070 and 900, respectively.[33]

Risk factors for vaginal cancer include:[29]

- Age (vaginal cancer occurs mainly in women age 60 and older)
- Oncogenic HPV infection
- A history of cervical precancers or cancer
- Smoking and alcohol use
- Immunosuppression

Vaginal precancers (Vaginal intraepithelial neoplasia, VaIN) are usually asymptomatic, although some patients experience increased or abnormal vaginal discharge. Symptoms of vaginal cancer include a vaginal mass, abnormal vaginal bleeding/discharge, dyspareunia and dysuria.[33,34]

HEAD & NECK CANCER

Most HPV-related head and neck cancers are squamous cell carcinomas of the oropharynx. Incidence and mortality or oropharyngeal cancer in the U.S. is estimated at 34,000 and 6,800, respectively.[35] Between 1998 and 2004 HPV-related oropharyngeal cancers increased by 225% in the U.S., compared to a 50% decrease in HPV-negative oropharyngeal cancers.[36]

Risk factors for oropharyngeal cancers include:[35]

- HPV infection. 60%-70% of oropharyngeal cancers are now thought to be associated with HPV, primarily involving one "high risk" genotype, HPV 16).[31,36]
- Gender (oropharyngeal cancers are more often diagnosed in males)
- Age (age 50 and older)
- Tobacco and alcohol use
- Immunosuppression

Symptoms of oropharyngeal cancers include persistent pain in the oral cavity, lumps or masses in the cheek or neck, dysphagia, pharyngitis, and chronic halitosis.[35]

PENILE CANCER

Virtually all penile cancers (> 95%) are squamous cell carcinomas. Other subtypes include verrucous carcinoma, adenocarcinoma, melanoma, and basal cell cancers.[37,38]

Penile cancers are rare in most of the developed world. Incidence and mortality in the U.S. is estimated at 1,820 and 310, respectively.[37]

Approximately half of penile cancers are associated with oncogenic HPV infection, particularly HPV 16.[39] Other etiological factors strongly associated with penile cancer include phimosis and balanitis (which many experts associate with higher penile cancer incidence in males who weren't circumcised in childhood).[40] Penile cancer is also more common in the immunosuppressed.

Penile cancers often present as lesions or masses on the glans penis or foreskin. Lesions, which may be flat or elevated, often are reddish in appearance, sometimes irritated or painful, and vary in size and distribution.[37,41]

PATIENT COUNSELING

PSYCHOSOCIAL ASPECTS OF HPV

A diagnosis of HPV and/or a related disease often carries a large psychosocial burden. Research indicates that having genital warts, for example, is associated with lower quality of life scores. Anxiety, depression, pain, and discomfort have been shown to be greater for patients with warts.[42] Specific complaints include frustration with treatment regimens, feelings of shame, and worries about relationships.[43]

Clinicians should be mindful that HPV diagnosis carries shame and stigma. In the 2015 STD treatment guidelines, the CDC recommends sharing the following information in patient counseling, as appropriate:[21]

- Anogenital HPV infection is ubiquitous among those who are sexually active, with a majority of men and women likely to have an HPV infection at some point; having genital HPV is a normal and expected consequence of human sexuality.
- The risk of HPV is similar in everyone, regardless of number of sex partners and history of other STDs; for this reason, Pap tests are equally important for all women, regardless of sexual history.
- The virus is usually harmless, causes no warts, abnormal Pap test, or any other apparent abnormality, and in most cases will clear naturally over a few months; however, it is difficult to determine how long an individual may be able to transmit the virus to new partners.
- Cancer is an uncommon outcome of infection, even with the oncogenic HPV genotypes.
- HPV diagnosed within a relationship should not be construed as an indication of infidelity
- It is rarely possible to determine when and from whom any particular HPV infection was acquired; in general, it is not important to identify the source of infection.
- HPV does not impact fertility and is unlikely to prevent a pregnant woman from having a normal vaginal delivery.
- Latex condoms are moderately effective at reducing the risk of HPV transmission for any single exposure; however, because condoms do not cover all vulnerable skin areas, they do not completely eliminate the risk.
- Sex partners of persons with diagnosed HPV infections do not need to be professionally examined and do not need to seek medical care unless and until they notice an abnormality, such as genital warts.
- Immunization should be routine for all sexually active young persons in order to prevent infection with the most troublesome HPV types

LINKS TO PROFESSIONAL RESOURCES

THE AMERICAN SEXUAL HEALTH ASSOCIATION

Counseling Patients on HPV
www.ashasexualhealth.org/healthcare-providers/videos

- Counseling Patients on HPV
- FAQs on HPV for Clinicians (with Dr. Hunter Handsfield)
- Recommending HPV Vaccines
- HPV Vaccines and Your Patients

THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

www.acog.org/

AMERICAN SOCIETY FOR CERVICAL PATHOLOGY AND COLPOSCOPY

Screening Guidelines for the Prevention and Early Detection of Cervical Cancer
www.asccp.org/Guidelines/Screening-Guidelines

2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors
www.asccp.org/portals/9/docs/asccp%20updated%20guidelines%20%20-%203.21.13.Pdf

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES RECOMMENDATIONS

9-valent HPV Vaccine
www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a3.htm

Quadrivalent HPV Vaccine
www.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm?s_cid=rr5602a1_e

Quadrivalent HPV Vaccine in Males
www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm

Bivalent HPV Vaccine in Females
www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a4.htm?s_cid=mm5920a4_e

CENTERS FOR DISEASE CONTROL AND PREVENTION

Human Papillomavirus (HPV) Infection
www.cdc.gov/std/tg2015/hpv.htm

Anogenital Warts
www.cdc.gov/std/tg2015/warts.htm

Reducing the Burden of HPV-associated Cancer and Disease
www.cdc.gov/mmwr/preview/mmwrhtml/mm6304a1.htm

2015 STD Treatment Guidelines
www.cdc.gov/std/tg2015/default.htm

AETC NATIONAL RESOURCE CENTER

Guide for HIV/AIDS Clinical Care: Anal Dysplasia
aidsetc.org/guide/anal-dysplasia

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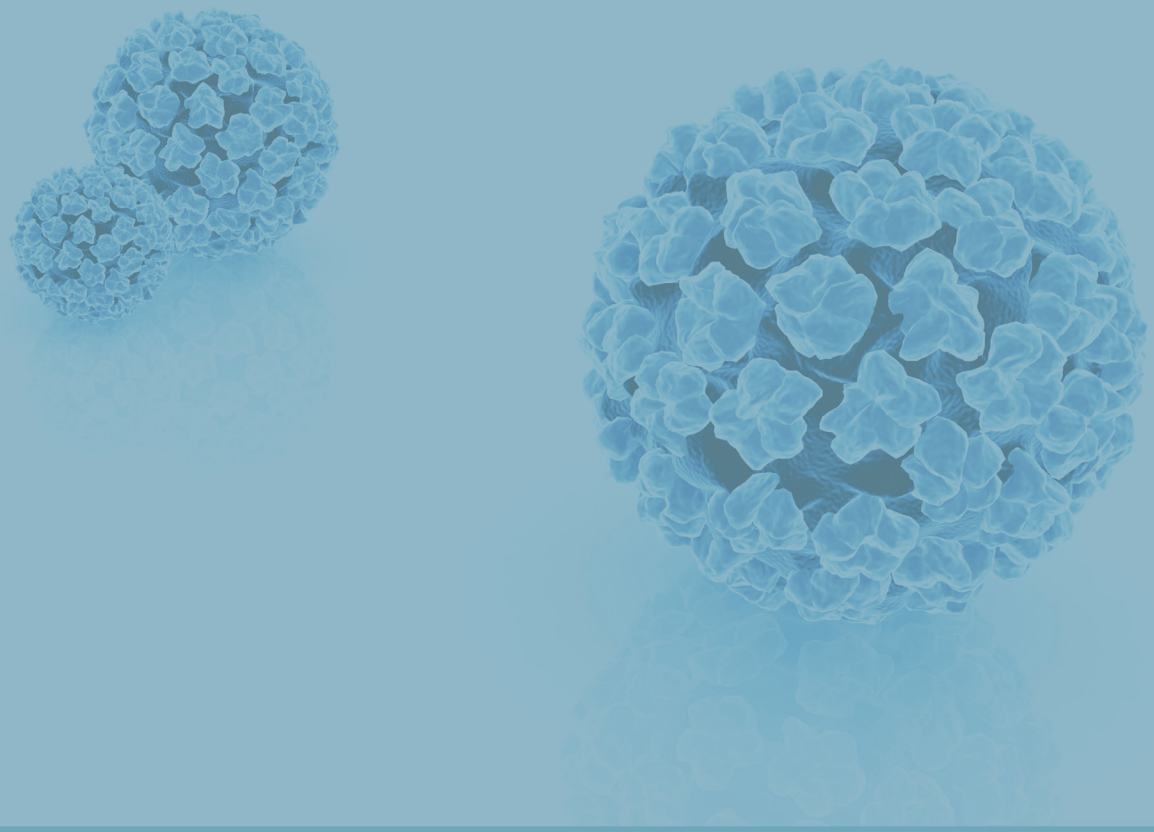

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