Understanding Anogenital HPV: Infections, Diseases and Vaccines in Male and Female Patients

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Human papillomavirus (HPV) infection is ubiquitous among sexually active individuals, and diagnosis of the virus and related diseases often carries a substantial psychosocial burden. After completing this educational activity designed for health care professionals, participants should be better able to:

- Provide education and counseling to patients about HPV infections, diseases, and vaccines
- Diagnose genital warts
- Treat genital warts appropriately with the full range of both patient- and provider-administered therapeutic options
- Recognize that HPV is common among sexually active people
- Offer vaccination as appropriate to prevent this common sexually transmitted disease that can cause cancer and other genital tract diseases

Introduction

Human papillomaviruses (HPV) are a group of double-stranded DNA viruses, over 100 types of which have been identified. Approximately 40 HPV types are associated with anogenital infections that are primarily acquired through sexual contact, particularly through vaginal and anal intercourse.[1,2] While uncommon, genital tract HPV is sometimes detected in persons with no reported history of sexual contact, although the exact route of transmission in such cases is not clear.[3] Additionally, recent data suggest that performing oral sex is a risk for oropharyngeal HPV infection.[4]

Anogenital HPV infections are nearly universal among sexually active individuals: data indicate up to 80% of sexually active persons experience one or more anogenital HPV infections.[5] The incidence of anogenital HPV infection in the United States is estimated to exceed 6 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 (SIL) that often are precursors to cancer.[6] Increasingly, data confirm a link between one oncogenic HPV type, HPV 16, and a subset of squamous cell carcinomas of the pharynx.[7] Non-oncogenic ("low risk" types) rarely cause cancer, but 2 low-risk types, HPV-6 and -11, cause approximately 90% of genital warts.[8] 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 sexually transmitted HPV and related diseases, especially within 2 prime areas of focus: cervical cancer and genital warts.

Cervical Cancer

The most clinically significant diseases associated with HPV are cervical precancers and cancers. Most cervical cancers originate in the cervical squamocolumnar junction (the transformation zone) and ~85% are squamous cell carcinomas, with the remainder largely glandular cell adenocarcinomas.[9]

There are approximately 1.4 million cases of mild cervical abnormalities (usually classified as low-grade SIL, or LSIL) in the United States each year.10 The estimated incidences of moderate to severe precancerous lesions (high-grade SIL, or HSIL) and cervical cancers are 500,000 and 12,700, respectively.[9,11] Mortality from cervical cancer exceeds 4,000 annually.[9] Cervical cancer tends to be diagnosed in women in the prime of life, with many cases among women in their 30s and a median age of 48 years when diagnosed.[12]

Globally, cervical cancer is most often detected in impoverished women, with 85% of cases occurring in the devel-

oping world where cost and health infrastructures have not permitted routine Pap testing.[13] As a result, cervical cancer–always the result of sexually acquired HPV infection–remains the fourth most common cause of cancer-related death in women throughout much of the world.[13] Rich nations are not immune to this, either: in the United States, racial and socioeconomic disparities in rates of cervical cancer are observed, with women of color far more likely to be diagnosed with cervical cancer and diagnosed at more advanced stages when the prognosis is poorer.[11,12]

The Role of HPV

Persistent infection with an oncogenic HPV type is the direct cause of cervical cancer and its precursors, and over 99% of cervical cancers contain the DNA of one or more high-risk HPV types.[2]

HPV infections become established in basal epithelium. Localized within these cells, the virus avoids immediate detection by the immune system and utilizes the life cycle of the cell to proliferate.[14] Mild cervical lesions and often precancerous ones typically develop in the months subsequent to HPV infection, while overt cancer usually is delayed many years.[15,16] According to the American Cancer Society, in the United States cervical cancer is most often detected in women who have either never had a Pap test, or in whom 5 or more years have lapsed since their last screening.[9]

HPV 16 and HPV 18, respectively, are the most oncogenic genotypes, and are found with 50% of moderate or severe pre-malignant cervical lesions, and in about 70% of invasive cervical tumors.[17]

Cervical Cancer Screening

Widely available Pap testing in the US has led to tremendous reductions in the incidence and mortality of cervical cancer. Once the leading cause of cancer death among women in the US, annual mortality per 100,000 women decreased from 5.55 in 1975 to 2.42 in 2007.[18] In the same interval, incidence dropped from 14.79 cases per 100,000 women to 6.58.[19]

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.[20] Several such tests are now on the market in the US 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.[20]
2. As a routine cervical cancer screening test in combination with a Pap test in women at or over age 30 (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.[21,22] Therefore, HPV infections in women over 30 years old are more likely to be a persistent infection and more likely to be associated with pre-malignant neoplasia or cancer, whereas most infections in younger women are transient and less likely to progress.23 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, than either test alone.[20]

Additionally, HPV 16/18 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.17 The potential advantage to genotyping may be to allow women who are high-risk HPV positive–but negative for the more aggressive HPV 16/18 types–to avoid immediate referral to colposcopy in favor of repeating Pap and HPV tests in 12 months.[24]

Onset of Cervical Cancer Screening and Intervals for Repeat Testing

Most HPV infections acquired in teens and young adults clear up spontaneously, including those caused by high-risk types.[21] It is now recognized that screening young women soon after onset of sexual activity results in large numbers of HPV infections and Pap tests abnormalities that can safely be ignored, but that historically have resulted in unnecessary treatment accompanied by preventable anxiety and stress. 23 Accordingly, the American College of Obstetricians and Gynecologists (ACOG) recommends cervical cancer screening not be initiated until age 21, regardless of age of first intercourse.

Recommended screening intervals depend largely on a woman's age and health history. ACOG recommends women aged 21-29 years be screened every 2 years. From age 30 and older, women can be screened at 3-year intervals providing they have at least 3 normal, consecutive Pap tests and are immunocompetent and have no past history of cervical cancer or precancerous lesions. The screening interval should also be 3 years when women 30 and older are screened with a cytology/HPV test combination and both tests are normal.[23]

Recent guidelines and recommendations call for more conservative approaches to screening adolescent women for cervical cancer and managing those under age 21 with abnormal cervical cancer screening tests.

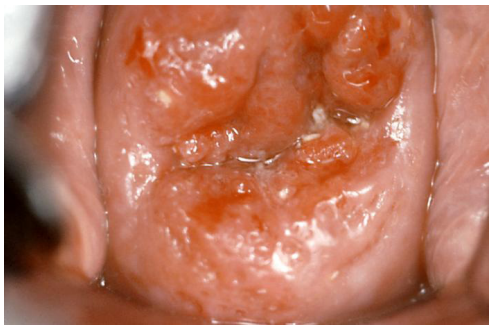

Image 1.Cervical erosions due to CIN 1.
Source: CDC; Public Health Image Library.

Managing Women with Abnormal Screening Tests

The evolution of screening technology has led to more nuanced management of women with abnormal cervical cancer tests. Clinical management is influenced primarily by the severity of the abnormality detected, but also is influenced by the patient's oncogenic HPV status and age: follow-up may involve simply monitoring the patient with repeat Pap and/or HPV tests at frequent intervals; colposcopy, or a diagnostic excisional procedure.20

Two systems of terminology are used to describe cervical cellular abnormalities, sometimes confusing to patients and providers alike: one applies to cervical cytology, (ie, Pap test results) and the other exclusively to biopsy results.

The Bethesda system, for cytology results, includes ASC-US, low-grade SIL (LSIL),high-grade SIL (HSIL), and cancer, as well as an intermediate stage between ASC-US and LSIL, called atypical squamous cells suspicious for high-grade changes (ASC-H); the terminology when biopsied tissue is examined microscopically is based on cervical intraepithelial neoplasia, or CIN.25 Cervical intraepithelial neoplasia -1, usually equivalent to LSIL, is mildly abnormal; most cases resolve without treatment and do not progress to cancer. CIN 2 and CIN 3, often difficult to distinguish from one another and hence combined as CIN 2/3, is more advanced and usually equivalent to HSIL. CIN 2/3 includes carcinoma in situ, the earliest stage of cancer. Figure 1 summarizes both systems and corresponding management guidelines published by the American Society for Colposcopy and Cervical Pathology (ASCCP).

BETHESDA SYSTEM[25]	CIN SYSTEM[25]	WHAT THE REPORT MEANS	ASCCP GUIDELINES[20]
Within normal limits		No abnormal cells, negative	Continue with normal screening
Atypical squamous cells of undetermined significance (ASC-US)		Cells that do not look entirely normal, but are not definitely abnormal. Most women with this Pap are normal, but a few will have HSIL.	Several options are available: 1) Repeat pap every 6 to 12 months until 2 Paps are normal. Any abnormal repeat Pap requires colposcopy. 2) Refer immediately for colposcopy (recommended with ASC-H). 3) Perform a HPV test. Women positive for HPV should have colposcopy. Women negative for HPV are likely normal and may safely be followed by Pap tests at 12 months. Women age 20 and under with a Pap reading of ASC-US should be managed with repeat Pap tests at 12 months.
Atypical squamous cells; cannot exclude high-grade SIL (ASC-H)		ASC-H: Similar to ASC-US reading, except the cells are abnormal in a way that means HSIL (see below) cannot be excluded.	
Low-grade SIL (LSIL)	CIN1	Mildly abnormal cells. Changes are most often due to HPV. Most women with this reading have mild cervical dysplasia, but some (10-30%) may have more abnormal changes (HSIL, moderate or severe dysplasia, CIN 2-3).	Colposcopy (and possibly biopsy) is the preferred follow-up option rather than repeat Pap testing or HPV testing. Most women with LSIL are positive for HPV and would not benefit as much from this test as women with ASC-US. Women age 20 and under with a Pap reading of ASC-US should be managed with repeat Pap tests at 12 months.
High-grade SIL (HSIL)	CIN2/3	Moderately to severely abnormal cells. Changes are almost always due to HPV. Most women with this Pap reading will have more abnormal findings on the cervix (HSIL, moderate or severe dysplasia, CIN 2/3).	Colposcopy and biopsy with treatment determined by biopsy results OR immediate diagnostic excisional procedure, such as loop electrosurgical excision procedure (LEEP) (this option is NOT acceptable for women age 20 and under).
Cancer	Invasive squamous cell carcinoma. Invasive glandular cell (adeno-) carcinoma.	The Pap will be read as suspicious for cancer if the cells are so abnormal as to indicate cancer. The possibility of cancer is high enough to require immediate evaluation .	Colposcopy and biopsy. Refer for a specialized evaluation and treatment as needed.

Figure 1. Reporting Terminology and Management Guidelines for Cervical Abnormalities.
Wright TC, et al.20; Apgar, et al.[25]

Genital Warts

At any point in time, around 1% of the US population is estimated to have anogenital warts.[26] Overall, it has been estimated that at 6% of US residents report a history of genital warts.5 Warts vary in appearance: most lesions are external, and can be raised(ie, "cauliflower" formation), or flat, single or multiple small or large. Typically, warts are asymptomatic but sometimes itch, bleed, or cause irritation.[5] Warts can be found in multiple anogenital sites including the vulva, vagina, cervix (less common), penis (including under the foreskin in uncircumcised males), scrotum, urethra, anus and perineum.[27] The groin and lower abdomen can be involved but this is uncommon.

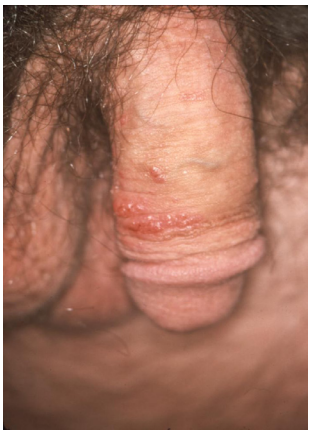

Image 2. Penile warts.
Source: Susan Lindsley/CDC; Public Health Image Library

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).[27] The currently available HPV tests are not approved nor recommended for diagnosis of warts. Application of acetic acid, which has been promoted as a diagnostic aid by highlighting the wart-involved tissues, is neither sensitive nor specific and is not recommended.[26]

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.[27] 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 is more effective than others in preventing recurrence.[5] When a particular treatment is not effective or if warts re-grow 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) 2010 STD Treatment Guidelines, except where noted.[27]

Patient-Applied Prescription Treatments

- **Podofilox (Condylox ®)**
  Podofilox is a purified derivative of podophyllin resin, and is available as a topical solution or gel.[28] 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 (Zyclara® 3.75% cream or Aldara® 5% cream)**
  Imiquimod is a topical immune response modifier. Zyclara is applied once daily for up to 8 weeks.[29] Aldara can be used 3 times a week (ie, 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.[29] Imiquimod is substantially less effective against warts on dry surfaces than those on moist surfaces, eg, the vulva or under the foreskin. Imiquimod has not been studied in pregnant women.[29]

- **Sinecatchins (Veregen®)**
  This extract from green tea is a recently approved treatment for genital warts. Available as an ointment, sinecatchins is applied to warts 3 times daily for as long as 16 weeks. Side effects include local irritation including rashes, itching, burning, and ulceration. Sinecatchins is contraindicated during pregnancy.

Provider-Applied Treatments

- **Trichloracetic acid (TCA) and bichloracetic acid (BCA)**
  Highly caustic acid compounds that are quite effective in rapidly ablating warts, but occasionally cause short but intense pain.5 Care must be taken to prevent contact with normal skin, and some providers protect the area around warts with petroleum jelly.30 Treatment can be repeated weekly, if necessary. Safe to use during pregnancy.28

- **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 appropriate for both external and internal warts, and for lesions on the cervix. Although pain at the application site is common (and, occasionally, scarring occurs where the treatment was applied to the wart), cryotherapy is generally well tolerated.30

- **Podophyllin resin**
  Efficacy of podophyllin may vary in part because of poorly and variable concentrations of the active compounds.5 Podophyllin is applied directly to warts, allowed to dry, and the patient is instructed to wash the compound away after 1 to 4 hours; treatment typically is applied weekly. Podophyllin is limited to external use and is contraindicated during pregnancy.

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

HPV Vaccines

The past decade has seen the development of 2 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 cause about 70% of cervical cancers; and the quadrivalent vaccine also is nearly 100% effective in preventing infection with HPV-6 and 11, which together are responsible for nearly all instances of genital warts.31 The characteristics of the 2 vaccines are listed in Table 1.

Table 1[31]
Characteristics of Bivalent and Quadrivalent Prophylactic HPV Vaccines

	Quadrivalent	Bivalent
Vaccine composition	20 µg HPV 6 40 µg HPV 11 40 µg HPV 16 20 µg HPV 18	20 µg HPV 16 20 µg HPV 18
Manufacturing process	Bread yeast (Saccharomyces)	Insect cells (baculovirus)
Adjuvant	225 µg aluminum hydroxyphosphate sulfate	500 µg aluminum hydroxide with 50 µg 3-deacylated monophosphoryl lipid A (AS04)
Preservatives	None	None

Vaccine Indications

The quadrivalent vaccine is approved for use in the United States in 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. The vaccine is also licensed for use in both males and females aged 9 to 26 years to prevent genital warts (condyloma acuminata) associated with HPV types 6 and 11, and anal cancers, precancers, and dysplasia caused by HPV types 6, 11, 16, and 18. The bivalent vaccine is approved for use in females aged 10 to 25 years for the prevention of cervical cancers and precancers associated with HPV 16 and 18. The emphasis on pre-teen and teen age groups is intended to maximize protection, because many HPV infections are acquired soon after onset of sexual activity.[21]

While the full duration or protection is not known, both vaccines produce antibody titer levels greater than the natural HPV infection, which appears to be protective.[2,32] With both of the currently available vaccines, immunogenicity and efficacy against diseases related to vaccine-types of HPV have been demonstrated for at least 5 years, but further research will be required to determine whether or not there is a role for booster immunization after that time.[32,33]

Efficacy

Both the quadrivalent and bivalent HPV vaccines are highly efficacious against significant cervical diseases (CIN 2/3 and AIS) related to the HPV types they help build immunity against (Table 2). The efficacy figures shown reflect the per-protocol analysis of those who received all 3 doses of the respective HPV vaccine and were seronegative and HPV DNA negative at baseline.

Table 2[31]
Bivalent and Quadrivalent HPV Vaccines: Efficacy in Females for Prevention of Cervical Intraepithelial Neoplasia (CIN) and Adenocarcinoma In Situ (AIS)

Vaccine/Endpoint/HPV Type	Vaccine Efficacy (confidence intervals)
Bivalent vaccine	
CIN 2/3 or AIS	
HPV 16 and/or 18	92.9 (79.9-98.3)
HPV 16	95.7 (82.9-99.6)
HPV 18	86.7 (39.7-98.7)
Quadrivalent vaccine	
CIN 2/3 or AIS	
HPV 16 and/or 18	98.2 (93.3-99.8)
HPV 16	97.6 (91.1-99.7)
HPV 18	100.0 (86.6-100.0)

The quadrivalent vaccine is also effective in preventing vaginal intraepithelial neoplasia (VaIN), vulvar intraepithelial neoplasia (VIN), genital warts, and anal intraepithelial neoplasia (AIN) caused by the 4 covered HPV types, as summarized in Table 3. The bivalent vaccine has not been studied in relation to these particular outcomes, but likely is similarly effective against lesions like VIN, VaIN, and AIN caused by HPV 16 or 18. However, the bivalent vaccine provides no significant protection against genital warts or other lesions caused by HPV 6 or 11.

Table 3[31]
Quadrivalent HPV Vaccine: Efficacy in Females for Prevention of Vulvar Intraepithelial Neoplasia (VIN), Vaginal Intraepithelial Neoplasia (VaIN), and Genital Warts

Vaccine/Endpoint/HPV Type	Vaccine Efficacy (confidence intervals)
VIN2/3 or VaIN2/3	
HPV 6, 11, 16 and/or 18	100.0 (82.6-100.0)
HPV 16	100.0 (76.5-100.0)
HPV 18	100.0 (<0-100.0)
Genital Warts	
HPV 6 and/or 11	99.0 (96.2-99.9)

The quadrivalent vaccine is efficacious in males in preventing anal intraepithelial neoplasia (AIN) and genital warts (Table 4).

Table 4[31,34]
Quadrivalent HPV Vaccine: Efficacy in Males for Prevention of Anal Intraepithelial Neoplasia (AIN) and Genital Warts

Vaccine/Endpoint/HPV Type	Vaccine Efficacy (confidence intervals)
Quadrivalent Vaccine	
AIN 1/2/3	
HPV 6, 11, 16, and 18	77.5 (39.6-93.3)
AIN 2/3	
HPV 6, 11, 16, and 18	74.9 (8.8-95.4)
Genital Warts	
HPV 6, 11, 16, and 18	89.3 (65.3-97.9)

HPV Vaccine Recommendations

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with either the quadrivalent or bivalent vaccine for all females ages 11 and 12 , with catch-up for those aged 13 to 26 years who have not previously been vaccinated.

For males, ACIP guidelines call for routine use of the quadrivalent vaccine in males ages 11 and 12, with catch-up for those aged 13-21 who have not received the vaccine.

HPV vaccines are recommended for use in adolescents for several reasons:

- The cervical transformation zone in girls and young women is particularly vulnerable to HPV infection.[35]
- HPV infection is most prevalent in females under 25 years of age; hence the obvious value of vaccinating against the virus prior to sexual debut.[22]
- Immunogenicity is higher in younger girls (9-15 years), as compared with 16-26 year olds.[2]

Dosing schedules with the vaccines are at 0, 1-2 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.[32,34]

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.[29,31] 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.[31]

Contraindications include:[31,32]

- 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)

While there is no evidence of impaired fertility/harm to the fetus in animal studies, HPV vaccines are contraindicated during pregnancy.[32] If a woman becomes pregnant after initiation of vaccination, the remainder of series should be delayed until postpartum. Lactating women can receive HPV vaccine.[31]

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 are have been shown to be greater for patients with warts, for example.[36] Specific complaints include frustration with treatment regimens, feelings of shame, and worries about relationships.[37]

Clinicians, then, should be mindful that HPV diagnosis carries shame and stigma. In the 2010 STD Treatment Guidelines, the CDC recommends sharing the following information in patient counseling, as appropriate.[27]

- 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 and many consistent condom users, perhaps most of them, acquire genital HPV somewhere along the line.
- 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.

Case Study

Introduction
An 18-year-old female patient comes to see you and brings her reluctant 19-year-old boyfriend. She is increasingly concerned about a cluster of slightly raised bumps on the coronal sulcus of his penis. He says they have been there for as long as he can remember. The couple occasionally uses condoms, and does not utilize any other type of contraception.

Her first intercourse was at age 15, and she has had three male sex partners prior to her current monogamous partnership for the past 6 months. Eighteen months earlier, she had warts detected around the anus, which were treated with cryotherapy and resolved.

The boyfriend's sexual debut was at age 13 or 14, and he recalls a history of at least 4 female sex partners and 1 male sex partner. He is reluctant to describe further details of his past sexual relationships, but confirms his partner's history of mutual monogamy in the past 6 months. He recalls having an HIV test a few years ago but never returned for results.

Physical Exam
The male's penile symptoms appear to be hirsutoid papillomas (pearly penile papules), a normal anatomic variant unrelated to HPV.

Lab Results
The female's most recent cervical cytology - 10 months ago at another clinic- detected mildly abnormal lesions (LSIL). She has had no follow-up.

Clinical Decision Point #1
Given the recent abnormal Pap test, what would be reasonable next steps in managing the female patient?

- ☐ Offer a Pap test now
- ☐ Offer a Pap test in 12 months
- ☐ Add HPV testing with any Pap test
- ☐ Combine colposcopy with the Pap test

Comment
While the recommendation is to delay cervical cancer screening until age 21, adolescent females are still sometimes given Pap tests. Given that HPV infections and related abnormalities typically regress naturally in young women, those under age 21 with borderline or mildly abnormal cervical cytology results should be followed with *repeat Pap testing at 12 months* rather than an immediate referral for colposcopy. If no high-grade disease (HSIL) is detected with the follow-up Pap test, repeat cytology again in 12 months.[20]

HPV testing is not recommended, given her age and the fact that a positive test result would not alter clinical management.

Additionally, the couple may benefit from:

- Birth control and STI counseling
- HIV testing
- Pregnancy and chlamydia tests for the female. Annual chlamydia testing is recommended for all sexually active females under age.[25,27]

Clinical Decision Point #2
To which of these 2 patients could you offer an HPV vaccine?

- ☐ Female only
- ☐ Male only
- ☐ Both male and female
- ☐ Neither

Comment
Both males and females can be vaccinated against HPV, although this is impacted in part by the type of HPV vaccine you offer. The bivalent vaccine is only approved for use in females aged 10 to 25 years, whereas the quadrivalent vaccine is approved for adolescent males and females aged 9 to 26 years. Regulatory standards do not prevent immunization in persons outside the approved population groups, although in some instances medical insurance may not cover such use.

The female patient has a previous diagnosis of 2 HPV-associated diseases (abnormal cervical cytology and anal warts), but by receiving either HPV vaccine she, benefits from protection against the HPV types covered by the vaccine to which she may not have been exposed. It is statistically unlikely she has already been infected by all the HPV types covered by the 2 vaccines.

References

1. Hernandez BY, Wilkens LR, Zhu X, Thompson P, McDuffie K, Shvetsov YB, Kamemoto LE, Killeen J, Ning L, Goodman MT. Transmission of human papillomavirus in heterosexual couples. *Emerg Infect Dis*. 2004;14: 888-894.
2. Markowitz LE, Dunne EF, Saraiya M, et al. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2007;56(RR-2):1-24.
3. Pao CC, Tsai PL, Chang YL, Hsieh TT, Jin JY. Possible non-sexual transmission of genital human papillomavirus infections in young women. *Eur J Clin Microbiol*. 1993;12:221-223.
4. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. Case-control study of human papillomavirus and oropharyngeal cancer. *N Eng. J Med*. 2007;356:1944-1956.
5. Handsfield HH. *Color Atlas and Synopsis of Sexually Transmitted Diseases. 3rd ed*. New York, NY: McGraw-Hill; 2011:133-148.
6. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118:3030-3044.
7. Ryerson AB, Peters ES, Coughlin SS, Chen VW, Gillison ML, Reichman ME, Wu X, Chaturvedi AK, Kawaoka K. Burden of potentially human papillomavirus-associated cancer of the oropharynx and oral cavity in the US, 1998-2003. *Cancer*. 2008;113:2901-2909.
8. American Society for Colposcopy and Cervical Pathology. Natural history of HPV. Available at http://www.asccp.org/PracticeManagement/HPV/NaturalHistoryofHPV/tabid/5962/Default.aspx. Accessed July 9, 2011.
9. American Cancer Society. Detailed Guide to Cervical Cancer. Available at http://www.cancer.org/Cancer/CervicalCancer/DetailedGuide/index. Accessed July 7, 2011.
10. Schiffman M and Solomon, D. Findings to date from the ASCUS-LSIL triage study (ALTS). *Arch Pathol Lab Med*. 2003;127:946-949.
11. Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, et al. American Cancer Society guidelines for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin*. 2007;57:7-28.
12. National Cancer Institute. Surveillance Epidemiology and End Results (SEER) Stat Fact Sheets: Cervix Uteri. Available at http://seer.cancer.gov/statfacts/html/cervix.html. Accessed July 7, 2011.
13. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global Cancer Statistics. *CA Cancer J Clin*. 2011;61:69-90.
14. Stanley M. Immune responses to human papillomavirus. *Vaccine*. 2006;24S1:S1/16-S122.
15. Winer RL, Kiviat NB, Hughes JP, Adam DE, Lee SK, Kuypers JM, et al. Development and duration of human papillomavirus lesions after initial infection. *J Infect Dis*. 2005;191:731-738.
16. Oster AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Path*. 1993;12:186-192.
17. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. *Int J Cancer*. 2007;121:621-632.
18. National Cancer Institute. Surveillance Epidemiology and End Results (SEER). Cancer of the cervix uteri: age-adjusted US death rates by year, race, and age. Available at http://seer.cancer.gov/csr/1975_2007/results_merged/sect_05_cervix_uteri.pdf. Accessed July 8, 2011.
19. National Cancer Institute. Surveillance Epidemiology and End Results (SEER). Cancer of the cervix uteri: Age-adjusted SEER incidence rates by year, race and age. Available at http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=5&page=sect_05_table.05.html. Accessed July 8, 2011.

20. Wright TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D for the 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *AJOG*. 2007;197:346-355.
21. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol. 2*002;55:244-265.
22. Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, et al. Prevalence of HPV infection among females in the US. *JAMA*. 2007;297:813-819.
23. American College of Obstetricians and Gynecologists (ACOG). Cervical cytology screening: ACOG practice bulletin 109. *Obstet Gynecol*. 2009;114:1409-1420.
24. American Society for Colposcopy and Cervical Pathology. HPV genotyping clinical update. Available at http://www.asccp.org/Portals/9/docs/pdfs/Consensus%20Guidelines/clinical_update_20090408.pdf. Accessed July 8, 2011.
25. Apgar BS, Zoschnick L, Wright TC. The 2001 Bethesda System Terminology. *Am Fam Physician*. 2003;15:1992-1998.
26. 2Centers for Disease Control and Prevention. Fact Sheet: Genital HPV. Available at http://www.cdc.gov/std/hpv/hpv-fact-sheet.pdf.
27. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010. *MMWR Morb Mortal Wkly Rep*. 2010;59(RR-12):70-74.
28. Kodner CM, Nasraty S. Management of genital warts. *Am Fam Physician*. 2004;70:2335-2342.
29. Imiquimod. [US prescribing information]. Graceway Pharmaceuticals, LLC.;2011.
30. Smith-McCune K. Therapeutic options for genital warts. Available at http://www.medscape.org/viewarticle/466158.
31. Centers for Disease Control and Prevention. FDA licensure of bivalent human papillomavirus vaccine (Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2010;59:626-631.
32. Cervarix. [US prescribing information]. GlaxoSmithKline:2009.
33. Garland SM, Hernandez-Avila M, Wheeler C, Perez G, Harper DM, Leodolter S, et al. Quadravalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007;356:1928-1943.
34. Gardasil. [US prescribing information]. Merck & Co., Inc.:2010.
35. Moscicki, AB. Impact of HPV infection in adolescent populations. *J Adolesc Health*. 2005;37:S3-S9.
36. Senecal M, Brisson M, Maunsell E, Ferenczy A, Franco EL, Ratnam S, Coutlee F, et al. Loss of quality of life associated with genital warts:baseline analyses from a prospective study. *Sex Transm Infect*. 2011;87:209-215.
37. Mortensen GL and Larsen HK.The quality of life of patients with genital warts:a qualitative study. *BMC Public Health*. 2010;10:1-8.