# Chapter 1
# Human Papillomavirus and Genital Warts

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## Introduction

Unknown until the second half of the twentieth century, human papillomavirus (HPV) is now recognized as being one of the most common sexually transmitted infections (STI) in the United States, accounting for more than one third of the new cases of STIs each year [1]. Most HPV infections cause no symptoms, other types can cause genital warts, and still others cause invasive squamous cell anogenital carcinoma. This chapter provides an overview of HPV infection—its transmissibility and epidemiology. It focuses on genital warts in its discussion of the clinical consequences of HPV infection and treatment options. The contribution HPV infection makes to various genital cancers is mentioned, but the screening, diagnosis, and treatments of these conditions are outside the scope of this book.

## Prevalence/Incidence

Precise estimates of the incidence of HPV infection are not available for several reasons. First, HPV is not a reportable disease. Additionally, most infections are subclinical. Of the patients who develop findings with HPV infection, most have

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only indirect indication of infections, such as abnormal cervical cytology. In patients who have more obvious manifestations of infection, such as external genital warts, no formal testing is done to document the presence of HPV. Finally, HPV also causes recurrent outbreaks of lesions. Because most first infections are asymptomatic, it may be difficult to recognize new cases from recurrent infections, which must be done to calculate incidence.

Prevalence of HPV infection is also difficult to estimate. The usual technique used to estimate the number of people infected with HPV is to measure serum antibodies. However, most people who acquire the viral infection clear that infection within 1–2 years; others may harbor the infection for years without outbreaks; others will have obvious recurrences. Some people in these groups will have positive antibody titers, so that antibodies may overstate the number of people who are currently infected (prevalence) [2]. Confusing the situation even further is the fact that only 50 % of individuals infected with HPV will develop detectable antibody titers to the virus, which could underestimate prevalence.

Despite these limitations, several studies performed over the past 20 years have demonstrated a steady rise in the number of new cases of genital HPV. The number of office visits for genital HPV disease has increased over the last 30 years [3]. It has been estimated that about 15 % (20–24 million) of adults in the United States are currently infected with this virus; 9.2 million of them are between the ages of 15 and 24 years [4–6]. The prevalence of HPV infection among sexually active college women over a 3-year period has been reported to be over 40 %; the greatest prevalence is among women with 3 or more lifetime partners or partners with 2 or more lifetime sexual partners [7–9].

## Risk Factors

Acquisition of HPV is clearly related to sexual activity. The highest risk groups for new infection are sexually active adolescents under the age of 19, followed by adults aged 19–30 [10]. The risk of HPV infection increases with number of lifetime sex partners. In one study, patients with 10 or more partners were found to have 58 % current infection rates compared with an 8 % rate in those with zero or one partner [11]. Risk factors for HPV acquisition are similar to those for other STIs, and include multiple recent sex partners and changing sex partners in the last year. Coinfection with other STDs and early age at first intercourse increase the risk of HPV infection. Expression of the virus and clearance of viral infection are related to immunocompetence of the host. Human immunodeficiency virus (HIV) infection increases the risk of HPV infection and the risk of developing HPV-related disease. All of the factors that predispose to persistent infection (those infections that do not clear) have not been elucidated. Persistent infections are associated with recurrent wart outbreaks and increase the risk of HPV-related malignancy.

## Infectivity and Transmission

HPV is most commonly transmitted during sexual activity, which involves skin-to-skin contact; microabrasions in the area of contact permit the virus to be transmitted from one sexual partner to another. Even in the absence of visible lesions, such as a genital wart, the microabrasions expose the HPV-infected cells in the basal epithelium of the host and increase viral shedding. More importantly, microabrasions in the recipient expose vulnerable basal epithelial cells to the virus. About 60–66 % of sex partners of HPV-infected people will develop detectable HPV lesions, although they may be very subtle appearing or may be located in areas that escape normal detection [12]. About 50–55 % of men whose partners have cervical HPV disease have HPV-associated penile lesions [13]. HPV can also be transmitted from one woman to another [14].

Oral–genital contact can transmit infection. Early studies suggested that about 4 % of women with external genital warts also had buccal lesions. High-risk HPV has been found in about 25 % of oral cancers, supporting hypothesis there is some transmission via that route [15].

Perianal infection is quite common. Transmission is possible in men and women who have anal receptive sex with men. However, the presence of genital warts around the anus does not necessarily indicate a history of receptive anal intercourse. In one study, only 10 % of women who shed HPV from the anal area admitted to having anal intercourse, and 83 % of those with virus in the anal area, were also positive for HPV in cervical, vulvar, and vaginal samples [16].

The virus can also be transmitted by fomites. Transmission of the virus to the anogenital area has been reported in tanning beds and saunas. Other nondirect transmission may be possible via sex toys, exam tables, door knobs, and contamination of exam lights adjusted by examining hands [17].

Vertical transmission from mother to her newborn is possible, though rare, during delivery through an HPV-infected birth canal. The most serious complication that occurs for the newborn is respiratory/laryngeal papillomatosis. Genital warts and facial lesions in the infant can also result from exposure during delivery. However, it is not yet clear that cesarean delivery prevents HPV transmission to the baby and should only be performed if genital warts obstruct the birth canal.

## Etiology

Papillomaviruses infect many animal species including cotton-tail rabbits, cattle, and humans. They are named and classified by their natural host. More than 120 different types of *human* papillomaviruses have been identified, but some have only been partially sequenced. HPV types are assigned new numbers when there is more than a 10 % difference in gene sequences in particular regions of the viral DNA and they

**Table 1.1** Low risk vs. high risk HPV types

| Low risk HPV types | High risk HPV types |
|---|---|
| Possess little to no oncogenic potential | Possess oncogenic potential |
| HPV 6,11,40,42,43,44,54,61,70,72,81 and CP6108 | HPV 16,18,31,33,35,39,45,51,52,56,58,59, 68,73,82 and probably 26,53,66 |
| Most commonly found on the external genitalia | Most commonly found as flat warts |
| Primarily responsible for external genital warts | Primarily responsible for intraepithelial neoplasias of the cervix, anus |
| Also responsible for juvenile respiratory papillomatosis | Also responsible for penile and anal carcinoma |

Adapted from Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papilloma-virus types associated with cervical cancer. N Engl J Med. 2003;348:518–27

are numbered in their order of discovery. All known HPV share a similar structure and genomic organization of small, non-enveloped virions with a double-stranded, circular DNA of 7800–7900 base pairs encased in an icosahedral protein capsid.

In general, genital HPV types have been classified into two groups based on the oncogenic potential—low- and intermediate/high-risk groups (*see* Table 1.1). The low-risk types (mainly 6 and 11) are responsible for almost half of the external genital warts. However, mixed viral types may be involved in the wart formation. The low-risk viral types have also been isolated from the lesions involved in laryngeal papillomatosis/respiratory papillomatosis in the tracheobronchial trees of children [18, 19]. The high-risk HPV types are primarily involved in the development of squamous cell cancerous lesions of the uterine cervix, anus, vulva, and penis [12, 20, 21], but also contribute to external genital warts. Four HPV types (6, 11, 16, and 18) account for 90 % of genital HPV infection.

## Clinical Course

The usual reservoirs of genital HPV infection are the moist mucosa and adjacent squamous epithelia of the male and female genitalia, the cervix, and the anus. Microabrasions that develop during sexual activity enable the infected partner to shed virus and the uninfected partner to become more susceptible to infection. Repeated trauma in the area increases infectivity as wound healing stimulates cell division, increasing episomal viral replication [22]. The virus enters the basal epithelial cells in areas such as the inner labia minora in woman and the prepuce and frenulum in men. Anal epithelium is also traumatized easily during sex, permitting HPV infection. The virus also preferentially infects the rapidly dividing cells within the transitional zone of the cervix.

After introduction of the virus into the host basal epithelial cells, the virus sheds its protein capsule and coexists within the host cell as a circular episome. The virus then enters into a latent incubation period of 1–8 months, during which time there

are no visible manifestations of the infection. The active growth phase starts when the first lesion develops. It is not known what induces the transition from latent to infective stage, but many host, viral, and environmental factors are involved. During the active infection phase, the HPV replicates independent of host cell division and induces the host cells to proliferate, creating a myriad of lesions from flat to papillary warts. Viral counts are highest in the superficial layers of the epithelium, increasing infectivity. During this phase, patients generally seek therapy.

Approximately 3 months later, the host immune system mounts a response. The innate immune system is recruited and interferons slow HPV replication and trigger the cell-mediated immune response. An immunocompetent cell-mediated immune system and cytokine production are needed for HPV clearance, but there are still challenges to viral clearance in immunocompetent hosts. HPV has some protection from the host response because the virus is intracellularly located. In addition, the epithelial cells in the perineum do not present antigens well to the host, so the HPV may not be recognized by the immune system [23]. HPV blocks the host response by depleting local intraepithelial lymphocytes, Langerhan's cells, and CD4+ cells and down regulating cytokine production [22]. However, lysis of the infected cells exposes the HPV to the host and triggers more intense defense.

About 80–90 % of people will clear the infection so that the virus can no longer be detected. Only 10–20 % of individuals will have persistent infection that can express itself either as a latent infection, which may be periodically reactivated, or as a persistent (and more difficult-to-treat) infection. Recurrences are more likely when host immune system is compromised by chemotherapy, corticosteroid therapy, or HIV infection.

## Clinical Manifestations

Genital warts can be found on the external genitalia, the vagina, cervix, anus, mouth, and larynx. Most patients with genital warts are asymptomatic. In a study of university women, neither acute nor persistent HPV infection (documented by viral shedding) was associated with discharge, itching, burning, soreness, or fissure [16]. Even women with genital warts had none of the associated symptoms. Patients with external genital warts may complain of a bump or mass they palpate or see on inspection. Infected or large lesions may be tender or associated with spotting, odor, or tenderness. Larger internal warts may produce dyspareunia or postcoital spotting. Urethral lesions may impair flow of urine or ejaculate. Condyloma acuminata are the classical external genital warts. They are raised, acuminate, exophytic lesions, which on keratinized skin are white, gray, or flesh-colored warty lesions. On mucosal surfaces, low-risk HPV tends to have finger-like projections and blend in color with surrounding tissue.

Another presentation of HPV in the genital area are papillomas. Papillomas are raised, possibly pigmented lesions, which are slow-growing and sometimes pedunculated. They are often mistaken for skin tags or moles and are most commonly found on keratinized skin.

The high-risk HPV usually causes flat genital warts. They may be hyperpigmented, white or red, depending on the impact HPV has on local melanocytes.

In women, external warts may present anywhere on the vulva, perineum, and perianal area. External genital warts in men may involve the squamous epidermis of the penis, foreskin, scrotum, perineum, and perianal area. Internal warts affect the mucous membranes of the urethra, anus, vagina, and oral cavity. Squamous cells on the cervix can also be involved as can the transitional epithelium of the urethra. Warts are most commonly located over areas that receive friction during coitus and therefore are found near the posterior fourchette of the vulva in women and around the corona of the penis in men. Oral HPV lesions are not common, but can be found in women with external genital warts.

The differential diagnosis for genital warts in women includes vestibular papillomatosis or micropapillomatosis labialis. These are congenital papillations that fill the vestibule with symmetric, smooth-contoured projections. One single projection arises from a base. In contrast, condyloma acuminata have multiple projections from one base and vary in size and distribution. The projections with vestibular papillomatosis may turn white after the application of acetic acid, but that observation does not confirm HPV infection, because there are many other causes of acetowhitening, including acute candidal infection, contact dermatosis, etc. In men, pearly penile papules that are found circumferentially around the tip of the penis may be misdiagnosed as HPV-related external genital warts. These normal papules are symmetrical and are located just under the corona and either side of the adjacent frenulum.

Other lesions that are in the differential diagnosis for the lesions caused by HPV include sebaceous cysts, molluscum contagiosum (especially in HIV-infected patients), and rudimentary hair shafts on the penis. For flat lesions, the differential diagnosis includes vulvar epithelial neoplasia, vaginal intraepithelial neoplasia, and cervical intraepithelial neoplasia depending on location. Condyloma lata, other dermopathies, and invasive carcinoma must also be considered.

## Diagnosis

Genital warts are commonly diagnosed by clinical examination. They may appear as typical peaked, cauliflower-like lesions; smooth papules; papules with a rough, horny layer; or as flat lesions. Testing for HPV is not useful in either the clinical diagnosis or the management of external genital warts. HPV testing for high risk types is only clinically useful for women being screened for cervical cancer. Further treatment guidelines for abnormal cervical cytology and histology results can be found through the American Society for Colposcopy and Cervical Pathology [24].

Biopsy of a suspicious lesion should be performed and sent for pathological analysis. Lesions are considered suspicious when they are surrounded by thickened skin, pigmentation, or unexplained ulcerations; raised, bleeding, red, or pigmented; indurated, fixed, or large (>2 cm); unresponsive to targeted therapy; and whenever a suspicion for malignancy exists. Warts in hosts who are immunocompromised

(HIV-infected) and/or who are at risk for HPV-related malignancy (chronic warts, heaving smoking) should also be biopsied. Biopsy is also indicated if the diagnosis is uncertain. Examination of other areas susceptible to infection is also necessary.

## Treatment of Genital Warts

Because warts can be disfiguring and prone to superinfection, treatment is generally recommended. However, it must be recognized that about 20–30 % of patients with genital warts will spontaneously clear the warts. In another 60 % of individuals, localized destruction of the wart will recruit host defenses and clear the HPV infection.

The goal of treatment is clearance of visible warts. Some studies show that treatment may reduce infectivity, but there is no evidence that treatment of warts reduces the risk for cancer or eliminates the virus [25]. Therapies can be used alone or in combination. Mechanical and chemical therapies can debulk large lesions and expose the virus to the immune system and prompt host response. Therapies that directly stimulate the local immune system are also available. An important part of all therapies is the patient education and counseling. HPV infection raises all the relevant questions generally associated with STIs, but adds concerns about potential long-term risks for cancer [26].

The CDC treatment guidelines separate the treatments for genital warts into two general categories: treatments that are patient-applied and those that are provider-administered. Factors that may influence selection of treatment include wart size, wart number, anatomic site of wart, wart morphology, patient preference, as well as cost of treatment, convenience, adverse effects, and provider experience [25–29].

It should be noted that warts on moist skin surfaces or intertriginous folds will usually respond to all treatments better than warts found on dry, keratinized skin [25]. Selection of a treatment modality should recognize that warts found on the keratinized skin of the circumcised penis or labia majora will probably require more treatment sessions than those found under the foreskin of the penis or on the inner folds of the labia minora. Most genital warts will respond within 3 months of treatment regardless of treatment modality chosen [25].

### *Patient-Applied Therapies*

#### Imiquimod 5 % Cream

Imiquimod is a topical cell-mediated immune response modifier that is recommended for treatment of external genital warts. The patient is instructed to apply a thin layer of cream to visible genital warts 3 times (alternating nights) per week at bedtime. It should be washed off 6–10 h after application [25]. Imiquimod is

provided in single use foil packets that can be used for up to 4 months as long as continued improvement is noted. For well-keratinized lesions, softening the surface of the wart by bathing and then disrupting it with vigorous drying with a towel has been suggested just before application. Imiquimod has a petroleum base and theoretically can weaken latex condoms or diaphragms. At any rate, sexual contact is not recommended when the cream is on the skin. Virtually all patients using the cream will develop localized erythema; however, only a small minority (10–15 %) has accompanying pain. The people who do experience pain can be advised to take brief holidays from the drug.

Imiquimod acts as a local immune modulator. It induces local interferon and cytokine release, which triggers both the innate and cell-mediated immune response systems [30, 31]. Complete clearance of warts occurs in 72–84 % of women with use of imiquimod but complete clearance rates in men are only half those seen in women [32]. However, many patients who do not completely clear all their lesions will have a substantial reduction in the numbers and size of remaining lesions. In clinical trials, 81 % of subjects had at least a 50 % reduction in wart area [31]. HPV recurrence rates after treatment with Imiquimod appear to be lower (5–19 %) than with other self-administered treatments [22]. Imiquimod is FDA pregnancy category C.

### Podofilox 0.5 % Solution or Gel

Podofilox contains purified extract of podophyllin and is recommended for the treatment of external genital warts not involving mucosal epithelium. The solution should be applied to the lesion with a cotton swab; the gel should be applied with a finger. To avoid irritation, the patient should allow the medication to dry after application before ambulating. Podofilox is applied to visible warts 2 times per day for 3 consecutive days, followed by 4 days of no therapy. This cycle may be repeated up to four cycles, as needed to clear warts. The total wart area treated at any application should not exceed 10 $cm^2$ and the total volume of podofilox applied should be limited to 0.5 mL per day. The mechanism of action of podofilox is to disrupt cell division. It arrests the formation of the mitotic spindle in metaphase and prevents cell duplication. It may also induce damage in local blood vessels and induce immune response by releasing interleukins. The safety of podophyllin during pregnancy has not been established [25]. Podofilox is currently listed as pregnancy category C.

## Sinecatechin Ointment 15 %

Sinecatechin ointment is a green-tea extract that was recently approved for the treatment of external anogenital warts. The mechanism of action is not well understood but probably related to green tea's antioxidative properties as well as potential antiviral and antitumor effects [33]. The ointment is applied to the area with a finger in

a thin layer daily and not washed off. It can be used until complete clearance of the wart, but for no longer than 16 weeks. Most common side effects are erythema, pruritis/burning, pain, ulceration, edema, induration, and vesicular rash and the ointment may weaken condoms and diaphragms [25]. In clinical trials, complete clearance of warts was obtained in up to 60 % of patients and recurrence rates were very low, 5–8 % [34–37]. Sinecatechin ointment has yet to be studied in comparison to the other patient applied therapies. It is not recommended for HIV-infected patients, immunocompromised patients including those with HIV, or those with clinical genital herpes as the safety and efficacy has not been established [25]. Safety in pregnancy has also not been established and it is currently listed as pregnancy category C.

## *Provider-Applied Therapies*

### Trichloroacetic Acid (TCA) 80–90 % or Bichloracetic Acid (BCA) 80–90 %

These acids coagulate the proteins within the wart and act as chemical cautery. They can be used for the treatment of warts on keratinized and mucosal epithelia. TCA or BCA is recommended for the treatment of external genital warts, vaginal warts, and anal warts. A small amount of TCA or BCA is applied directly to visible warts and is allowed to dry. With treatment, the wart will immediately develop a white "frosting" color. Over the ensuing days to weeks, if successful, the wart will detach and leave an ulcer behind. This may be painful and must be monitored for infection. These complications limit the number of warts treated at a single session.

To ensure accurate placement of the acid on the wart, the blunt end of a wooden cotton-tipped applicator or a urethral swab can be used. If a very small area is to be treated, the wooden stick of a cotton-tipped applicator can be broken to reveal a pointed end. Building a moat of lidocaine ointment around the lesion prevents seepage into the surrounding area and provides some comfort. Other health care providers suggest that applying a small amount of lubricating jelly to the treated warts after treatment with TCA or BCA may contribute to patient comfort.

Care must be taken to avoid contamination of the clean bottle of TCA or BCA by using a new applicator stick each time, therefore an adequate supply of applicators of choice should be readily available. If excessive acid is applied to the patient, the health care provider can use either some talc, sodium bicarbonate (i.e., baking soda), or liquid soap to remove excessive acid [25]. This must be applied immediately because the acid will cause burns in a matter of seconds. Therefore, access to these basic substances should be readily available.

In addition, because TCA and BCA are highly caustic agents they must be stored in an area away from children's reach. Containers of TCA and BCA must also be properly labeled, and all staff working with this substance must be properly educated to avoid confusing these highly caustic agents with acetic acid (vinegar).

Clearance rates of up to 80 % can be expected, but multiple applications at weekly intervals may be made. TCA and BCA are not absorbed into systemic circulation and are safe to use during pregnancy.

### Podophyllin Resin 10–25 % Sodium

This chemical is compounded in a tincture of benzoin that is cytotoxic and antimitotic and induces tissue necrosis. Podophyllin is recommended for the treatment of external genital warts and urethral meatus warts. A small amount of the solution is applied to each wart on the external genital and allowed to air-dry to prevent irritation. Treatment can be repeated weekly as needed. Podophyllin is neurotropic; it should not be applied to mucosal surfaces from which it might be systemically absorbed. Moreover, application must be limited to less than 0.5 mL or an area of less than 10 $cm^2$ of warts per session [25]. Some specialists recommend it be washed off 1–6 h after application to reduce the chance of a local irritation and inflammation. Podophyllin should not be applied to the cervix, vagina, oral cavity, or anal canal. The safety of podophyllin during pregnancy has not been established.

## Cryotherapy

Cryotherapy freezes the water within the mitochondria of the cell and causes thermally induced cytolysis. Clinicians can use liquid nitrogen (applied by cotton-tip applicator or spray) or nitrous oxide applied by cryoprobes. Regardless of the device used to deliver the cryotherapy to the lesion, application to the wart should continue until the ice ball has extended approximately 2 mm from the edge of the wart. The lesion is then allowed to thaw. Many providers have found that a second freeze session improves efficacy. It has been shown that the tissue destruction occurs during the thawing portion of this process, so adequate time must be given between the freeze–thaw sessions [28]. Cryotherapy is safe to use during pregnancy.

Liquid nitrogen is recommended for the treatment of external genital warts, vaginal warts, urethral meatal warts, anal warts, and oral warts. If the liquid nitrogen is obtained from a large metal tank, it evaporates quickly; a large portion of the expense comes from frequent refilling of this large tank. A metal ladle is supplied, which is used to fill either the sealed spray canister or Styrofoam cup. Care must be taken when ladling the liquid nitrogen and protective hand coverings should be worn at all times to protect the exposed skin of the health care provider. A Styrofoam cup is used because of its excellent insulation properties; other materials are not as reliable. Regular cotton-tipped applicator sticks are used to apply the liquid nitrogen to the genital wart. Depending on the size of the lesion, it may be useful to form the cotton tip into a point before dipping it into the nitrogen.

When the nitrogen spray canister is used, it is important that the health care provider have excellent hand–eye coordination so that a steady stream of liquid

nitrogen is directed at the lesion only, sparing unaffected surrounding tissue. This will take practice to become proficient, especially when treating small warts.

Nitrogen also comes as compressed gas form (nitrous oxide), which is attached to a cryoprobe with a tip that matches the size and shape of the wart. This is the same handheld cryoprobe used to treat cervical dysplasia. Gaseous nitrogen is recommended for the treatment of external genital warts. A small amount of lubricating jelly may be applied to the cryoprobe or to the genital wart to help transfer the cold to the lesion. The trigger is pulled back, allowing the refrigerant to enter the gun, which freezes the tip and the jelly covering the wart. Because the freezing is more intense and less controlled with the cryoprobe, it is not recommended for use in cryotherapy of lesions on their mucosal surfaces such as the urethra or vagina.

Overall, clearance rates with cryotherapy are up to 90 %, recurrence rates approach 40 % [38].

## Surgical Therapies

In general, this therapy is reserved for large or medium lesions and those that are unresponsive to medical therapies. The warts are removed at the dermal–epidermal junction. Various techniques that can be used in different settings include scissor excision, shave excision, curettage, LEEP, electrocautery, and laser. Treatment may lead to scarring and vulvodynia if too deep a removal is performed, especially with LEEP. Often surgical excision is done under local anesthesia and requires specialist training.

However, surgical excision can be easily performed in the office to remove a wart that is pedunculated on a slender (1–2 mm) stalk. This type of wart is quite commonly seen in perianal area. After cleaning the area, lift the wart, visualize the separation line between the epidermis and the wart and cut across the base of the lesion along that line. Hemostasis is generally easily obtained by pressure and the use of Monsel solution or other chemical styptic.

Carbon dioxide laser therapy may be useful for extensive vulvar warts and anal warts, especially if other therapies have failed. It is also the preferred treatment for immunocompromised, nonpregnant patients with large lesions. All the lesions may be destroyed in one treatment, although healing may be uncomfortable. Laser therapy has been associated long-term with vulvodynia, particularly if the deeper tissue layers are burned. Recurrence rates are low in the immediate posttreatment period.

## Alternative Therapies

The CDC treatment guidelines also offer a few alternative regimens including intralesional interferon, photodynamic therapy, and topical cidofovir. These regimens are considered alternates as they may cause more side effects or have limited efficacy data [25, 26].

## Combination Therapies

The CDC treatment guidelines note that because each of the available treatments has shortcomings, some clinics employ combination therapy (i.e., the simultaneous use of two or more modalities on the same wart at the same time) [25]. As data is limited on the efficacy and risk of this practice, clinicians may want to use different treatment modalities sequentially. For example, a clinician may start therapy with TCA and have the patient return later for cryotherapy to remove persistent lesions. In another approach, at least one study has demonstrated the efficacy of up to 16 weeks of treatment with imiquimod followed by surgical removal of any remaining genital warts; recurrence rates were also reduced [39].

## Patient Education and Counseling

The psychological impact of diagnosis of HPV infection may be even more profound than that of other STIs. In addition to issues of relationship fidelity, there is the issue of oncogenic potential, which requires additional counseling [40].

College-aged women are at particularly high risk for acquiring HPV infection. The diagnosis can cause confusion and distress for women; they may need psychological support and information from their health care provider. Patients with HPV on pap smears report that the diagnosis created a negative effect on their sexual contact and on their relationship with their partner [41, 42]. One large study of patients with HPV found that a majority rated their provider as fair or poor in counseling them [43]. Patients were most disturbed by the lack of advice about emotional issues. Survey of clinicians in college-based clinics recognized the patient's need for information but 46 % spent less than 10 min providing education and counseling to newly diagnosed patients [40].

Patients often may ask how long the infection has been there and when and where was the infection acquired. It is not possible for the clinician to answer these questions accurately. The HPV infection may be subclinical (without visible lesions) for many months or years. A period of decreased immunity (as seen in pregnancy) or increased stress may trigger the growth of warts. It is important for the patient to understand three other points:

- Genital HPV infection is common among sexually active adults.
- Genital HPV infection is usually sexually transmitted, but the sex partner probably is not aware that infection is present.
- HPV testing is not warranted for the patient or the partner.

## Follow-up

Follow-up at 3 months can be offered to patients who have cleared anogenital warts. This will provide an opportunity to evaluate for recurrent warts and to continue to provide patient education. Female patients who have had a history of anogenital warts should be advised to receive annual pap smears to evaluate for cervical abnormalities. Self-examination for external genital warts may be encouraged.

## Partner Notification and Reporting Requirements

There is no legal requirement to notify sexual contacts. It is known that most sex partners of individuals infected with HPV are themselves infected. There is no documented evidence that professional examination of sex partners is necessary. Treatment of the partner has not been shown to reduce the patient's risk for recurrence. Recurrence of anogenital warts can result from reactivation of a latent infection. For these reasons, the CDC treatment guidelines do not mandate partner notification or treatment in the absence of grossly visible lesions. However, it should be noted that a visit to a health care provider affords an excellent opportunity to provide education and to screen for other STIs in all patients. Female partners of men with external genital warts should be encouraged to receive routine pap smears [25].

## Pregnancy-Related Issues

During pregnancy, HPV tends be expressed or reactivated, potentially due to a pregnant woman's relative immune system suppression. This does not necessarily mean a recent inoculation/infection with HPV, but probably represents a latent infection or a reactivation of an old infection. The incidence of laryngeal papillomatosis in infants and children is extremely rare and the mechanism of transmission is not entirely understood. Despite the possibility of vertical transmission, vaginal delivery is the preferred method of delivery for women with genital warts. However, occasionally, a cesarean section will be recommended when extensive lesions obstruct the outlet of the birth canal or they create a concern that laceration/episiotomy repair would not be possible [25]. Treatment of external genital warts during pregnancy is generally advocated because the lesions tend to grow in the immunocompromised state and may become superinfected although wart resolution may be incomplete. Imiquimod, sinecatechins, podophyllin, and podofilox should not be used and tiny asymptomatic lesions may not warrant treatment.

## HIV-Related Issues

People infected with HPV are both more likely to develop genital warts and to have more difficult-to-treat warts than people without HIV. While there is no data to suggest specific treatment modalities for the HIV-infected patient, it should be noted that they might not respond as well to therapy or be prone to more frequent wart recurrences [25].

## Prevention

There are currently two HPV vaccines licensed for use in the United States: a quadrivalent vaccine (Gardasil) and a bivalent vaccine (Cervarix). Both vaccines provide protection against HPV 16 and 18, responsible for about two thirds of all cervical cancers while Gardasil also targets HPV types 6 and 11 found in nearly 90 % of anogenital warts. Both vaccines are given in a 3 dose series at 0, 2, and 6 months. Either can be given to girls aged 9–26 [44, 45] while the quadravalent vaccine can also be used in boys 9–26 years old to prevent genital warts [46]. Vaccinated women not previously exposed to these HPV types are expected to have a 90 % reduction in genital infection from those HPV types [47–49].

The vaccines should ideally be administered before the onset of sexual activity but should still be offered after sexual debut. Furthermore, women who have received HPV vaccination should continue routine cervical cancer screening as HPV types 16 and 18 account for only 70 % of cervical cancers.

Avoiding skin-to-skin contact with an infected partner is the most effective approach to prevent HPV infection. Condom use has been shown to protect against the acquisition of genital HPV infection. A study of newly sexually active college women showed a 70 % risk reduction in HPV transmission with correct and consistent condom use [50]. Furthermore, condom use reduces HPV-related diseases, such as genital warts in men and cervical dysplasia in women and is associated with higher rates of regression of these conditions [13, 51].

## References

1. The Henry J. Kaiser Family Foundation. Fact sheet: sexually transmitted diseases in the U.S. Available from: http://www.kff.org/womenshealth/1447-std_fs.cfm. Accessed 31 Dec 2012.
2. Gerberding JL. Report to congress: prevention of genital human papillomavirus infection. Atlanta, GA: Centers for Disease Control and Prevention, Department of Health and Human Services; 2004.
3. The Centers for Disease Control and Prevention. 2011 Sexually transmitted diseases surveillance table; 2011. Available from: http://www.cdc.gov/std/stats11/tables/44.htm. Accessed 31 Dec 2012.

4. Cates Jr W. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. Sex Transm Dis. 1999;26:S2–7.
5. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol. 2000;151:1158–71.
6. Weinstock H, Berman S, Cates Jr W. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Perspect Sex Reprod Health. 2004;36:6–10.
7. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med. 1998;338:423–8.
8. Silins I, Kallings I, Dillner J. Correlates of the spread of human papillomavirus infection. Cancer Epidemiol Biomarkers Prev. 2000;9:953–9.
9. Sellors JW, Mahony JB, Kaczorowski J, et al. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. Survey of HPV in Ontario Women (SHOW) Group. CMAJ. 2000;163:503–8.
10. Sellors JW, Karwalajtys TL, Kaczorowski J, et al. Incidence, clearance and predictors of human papillomavirus infection in women. CMAJ. 2003;168:421–5.
11. Bauer HM, Hildesheim A, Schiffman MH, et al. Determinants of genital human papillomavirus infection in low-risk women in Portland, Oregon. Sex Transm Dis. 1993;20:274–8.
12. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348:518–27.
13. Bleeker MC, Hogewoning CJ, Voorhorst FJ, et al. Condom use promotes regression of human papillomavirus-associated penile lesions in male sexual partners of women with cervical intraepithelial neoplasia. Int J Cancer. 2003;107:804–10.
14. Marrazzo JM, Koutsky LA, Stine KL, et al. Genital human papillomavirus infection in women who have sex with women. J Infect Dis. 1998;178:1604–9.
15. Cox T, Buck HW, Kinney W, Rubin MM. HPV types: natural history and epidemiology. Human papillomavirus (HPV) and cervical cancer. Clinical proceedings. Washington, DC: Association of Reproductive Health Professionals; 2001. Available from: org/healthcareproviders/onlinepublications/clinicalproceedings/cphpv/types.cfm?ID=149. Accessed 24 Nov 2006.
16. Mao C, Hughes JP, Kiviat N, et al. Clinical findings among young women with genital human papillomavirus infection. Am J Obstet Gynecol. 2003;188:677–84.
17. Perniciaro C, Dicken CH. Tanning bed warts. J Am Acad Dermatol. 1988;18:586–7.
18. Blackledge FA, Anand VK. Tracheobronchial extension of recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol. 2000;109:812–8.
19. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol. 2003;101:645–52.
20. Byars RW, Poole GV, Barber WH. Anal carcinoma arising from condyloma acuminata. Am Surg. 2001;67:469–72.
21. Rubin MA, Kleter B, Zhou M, et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. Am J Pathol. 2001;159:1211–8.
22. Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. Am J Obstet Gynecol. 2003;189:S3–11.
23. Arany I, Evans T, Tyring SK. Tissue specific HPV expression and downregulation of local immune responses in condylomas from HIV seropositive individuals. Sex Transm Infect. 1998;74:349–53.
24. American Society for Colposcopy and Cervical Pathology. Consensus guidelines: cytology algorithms and HPV genotyping algorithm. Available from: http://www.asccp.org. Accessed 5 Jan 2013.
25. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2010. Available from: http://www.cdc.gov/std/treatment/2010/genital-warts.htm. Accessed 31 Dec 2012.

26. Lacey CJ. Therapy for genital human papillovirus-related disease. J Clin Virol. 2005;32 Suppl 1:S82–90.
27. Langley PC, Richwald GA, Smith MH. Modeling the impact of treatment options in genital warts: patient-applied versus physician-administered therapies. Clin Ther. 1999;21:2143–55.
28. Kodner CM, Nasraty S. Management of genital warts. Am Fam Physician. 2004;70:2335–42.
29. Lacey CJ, Goodall RL, Tennvall GR, et al. Randomized controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. Sex Transm Infect. 2003;79:270–5.
30. Dahl MV. Imiquimod: an immune response modifier. J Am Acad Dermatol. 2000;43:S1–5.
31. Tyring SK, Arany I, Stanley MA, et al. A randomized, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod. J Infect Dis. 1998;178:551–5.
32. Edwards L, Ferenczy A, Eron L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol. 1998;134:25–30.
33. Melzer SM, Monk BJ, Tewari KS. Green tea catechins for treatment of external genital warts. Am J Obstet Gynecol. 2009;200:233.e1–e7.
34. Tatti S, Swinehart JM, Thielert C, et al. Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. Obstet Gynecol. 2008;111:1371–9.
35. Tzellos TG, Sardelli C, Lallas A, et al. Efficacy, safety and tolerability of green tea catechins in the treatment of external anogenital warts: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2011;25(3):345–53.
36. Stockfleth E, Beti H, Orasan R, et al. Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. Br J Dermatol. 2008;158:1329–38.
37. Gross G, Meyer KG, Pres H, et al. A randomized, double-blind, four-arm parallel-group, placebo-controlled phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. J Eur Acad Dermatol Venereol. 2007;21:1404–12.
38. Maw RD. Treatment of anogenital warts. Dermatol Clin. 1998;16:829–34.
39. Carrasco D, vander Straten M, Tyring SK. Treatment of anogenital warts with imiquimod 5% cream followed by surgical excision of residual lesions. J Am Acad Dermatol. 2002;47:S212–6.
40. Linnehan MJ, Groce NE. Psychosocial and educational services for female college students with genital human papillomavirus infection. Fam Plann Perspect. 1999;31:137–41.
41. Campion MJ, Brown JR, McCance DJ, et al. Psychosexual trauma of an abnormal cervical smear. Br J Obstet Gynaecol. 1988;95:175–81.
42. Filiberti A, Tamburini M, Stefanon B, et al. Psychological aspects of genital human papillomavirus infection: a preliminary report. J Psychosom Obstet Gynecol. 1993;14:145–52.
43. Guy H. Survey shows how we live with HPV. HPV News. 1993;3(1):4–8.
44. CDC. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep. 2007;56(No. RR-2):1–24.
45. CDC. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep. 2010;59:626–9.
46. CDC. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep. 2010;59:630–2.
47. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med. 2002;347:1645–51.
48. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet. 2004;364:1757–65.

49. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol. 2005;6:271–8.
50. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med. 2006;354:2645–54.
51. Hogewoning CJ, Bleeker MC, van den Brule AJ, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. Int J Cancer. 2003;107:811–6.