Genital Human Papillomavirus (HPV) Infections

January 2008

GENITAL HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS

This chapter covers the prevention, diagnosis and treatment of human papillomavirus infection. For complete information on the prevention, diagnosis and treatment of cervical cancer, other sources should be used.

Etiology

Definition

- Human papillomavirus (HPV) causes skin or mucosal infections and has a strong affinity for the moist mucosa of the anal, genital and aerodigestive tracts.

Etiology

- More than 130 HPV types have been classified on the basis of DNA sequence, 40 of which can infect the anogenital epithelium. HPV types are classified as high- or low-risk based on the strength of their association with cervical cancer.

Table 1. HPV types

Association with cervical cancer[1]	Genotypes	Most likely clinical conditions
Low-risk	• Most common: 6 and 11 • 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108	Condylomata acuminata
Probable high-risk	• 26, 53 and 66	Precancerous or cancerous lesions
High-risk	• Most common: 16, 18 • 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82	Precancerous or cancerous lesions

Epidemiology

- HPV is one of the most common sexually transmitted infections (STIs).[2]
- The incubation period for exophytic warts is 1–8 months.
- 70% of the adult population will have had at least one genital HPV infection over their lifetime.[3]
- Canadian HPV prevalence studies show that HPV infection is very common and that wide variability exists between different populations:
  - In young women, prevalence is reaching 29%.[4,5]
  - In a community health centre in Manitoba where 73% of participants were <30 years, 33% of women were found to be HPV-positive.[6]
  - In women aged 15–49, attending for routine cervical cancer screening in Ontario, the prevalence of high-risk HPV was found to be 12.7%.[7,8]
  - In women aged 13–79, attending for routine cervical screening in Nunavut, the prevalence of high-risk HPV was found to be 25.7%.[9]
- HPV infections are often acquired early (15–19 years of age),[10] and the majority (>80%) of these infections clear spontaneously within 18 months.[11]

- HPV infections usually occur in adolescents and young adults, but affect both women and men of all ages.
- Non-oncogenic or low-risk HPV, which can be expressed as exophytic warts, is associated with a low risk for cancer.
- Clinically visible external genital warts (EGWs) (with low-risk HPV) were noted in ~1% of sexually active adults (aged 15–49) in a U.S. population.[12]
- **Thirteen high-risk HPV types have been confirmed in the International Agency for Research on Cancer monograph on cervical cancer screening as necessary factors in the etiology of cervical cancer, while other HPV types have been implicated in skin and oral-pharyngeal cancers, as well as with cancers of the anus and penis.**[13]
- The average time from acquiring a high-risk genotype of HPV to the detection of cervical cancer is 20 years.[14]
- Infection with one HPV genotype does not protect against infection with other types.[15,16]
- Simultaneous infection with multiple types of HPV has been reported in 5–30% of women with HPV.[17]
- Symptomatic perinatal transmission is infrequent and is usually clinically apparent within 2 years. When it occurs, it is associated with anogenital and vocal-cord lesions in the newborn.[18]

Prevention

- Discuss HPV vaccine with women as per the recommendations outlined in the Canada Communicable Disease Report, Volume 33 ACS-2, (2007) *National Advisory Committee on Immunization (NACI) statement on Human papillomavirus vaccine*.
- While condoms may not reliably prevent sexual transmission of HPV, they may protect against the HPV types of genital warts,[19] some co-factors of cervical dysplasia and invasive cervical cancer; in addition, they effectively prevent transmission of bacterial STIs.
- Counsel patients with HPV infection about risk reduction, including the following:
  - Natural history of the disease, with emphasis on the differences between HPV genotypes and their potential manifestations.
  - Potential for recurrent episodes.
  - Potential for sexual transmission.
- There are conflicting epidemiologic data on risk factors and co-factors for HPV infection. The only factor that emerges consistently is lifetime number of sex partners. Putative co-factors for cervical cancer include the following:
  - Smoking tobacco and exposure to tobacco smoke.
  - Long-term use of oral contraceptives (>5 years).
  - Higher number of pregnancies.
  - Other STIs (e.g., *Chlamydia trachomatis*, herpes simplex virus-2, HIV).
  - Inadequate diet (especially low antioxidant intake).
  - Immunosuppression (e.g., HIV/AIDS, organ transplant and immunosuppressive drug therapy).
  - Multiple sex partners, sexual intercourse at an early age and sexual intercourse with those infected with HPV.
  - Genetic susceptibility: polymorphisms in certain cell regulatory genes, such as *p53*.

Information about HPV[20–23]

- Inform women that regular cervical screening for dysplasia and/or HPV infection is effective in reducing rates of cervical cancer.[24–26]
- Counselling for patients with HPV and/or abnormal cervical screening results should include the following:
  - Explanation of the natural history of the disease, with emphasis on the differences between types of HPV and their causal associations (i.e., low-risk types are associated with anogenital warts, and high-risk types are associated with cervical cancer).
  - Discussion of the risk of recurrence.
  - Reduction of the impact of risk and co-factors for progression to dysplasia.
  - Encouragement of patients to examine themselves and seek medical attention if lesions appear.
  - Reassurance that the virus is common, and that it is virtually impossible to determine when or from whom they acquired the virus.
  - Reassurance that the risk of cervical cancer is quite low and that most HPV infections will resolve and clear.
  - Reassurance that only persistent infection with high-risk HPV types may progress to precancerous and cancerous lesions.

Diagnosis

- Most anogenital HPV infections are asymptomatic and subclinical. Of those clinically apparent lesions, most will be asymptomatic.
- The most frequent sites of anogenital HPV infection in females are the cervix, vagina, vulva or anus.
- The most frequent sites of anogenital HPV infection in males are the anus or penis.
- Multiple sites are often involved (e.g., cervix, vagina, vulva etc.).
- The natural history is of fluctuation in size and number of warts and, in most cases, eventual clearance.
- Warts can increase in size and number with pregnancy.
- Intraepithelial lesions on a Pap smear usually indicate cervical involvement. These are classified as one of the following:
  - Low-grade squamous intraepithelial lesions (LSILs): under the old classification system, these were known as condyloma of the cervix, mild to moderate dysplasia or cervical intraepithelial neoplasia (CIN) 1 or CIN2.
  - High-grade squamous intraepithelial lesions (HSILs): under the old classification system, these were known as severe dysplasia, CIN3 or *in situ* neoplasia.
  - Invasive carcinoma.

External genital warts[27]

- Most EGWs are caused by low-risk HPV infections.
- Typical EGWs present as exophytic fronds or cauliflower-like to papular growths on anogenital skin and/or mucous membrane called condylomata acuminata. They are frequently multiple, asymmetric and polymorphic. They occasionally cause bleeding, pruritus and local discharge.
- Less frequent manifestations of EGWs are slightly elevated lesions, papular or macular lesions with or without keratinization and/or brown/grey/bluish pigmentation, also known as bowenoid papulosis, or warty vulvar intraepithelial neoplasia.

Table 2. Non-HPV lesions to consider in a differential diagnosis

Normal variations	• In both sexes: sebaceous glands • In women: vestibular papillae, also known as micropapillomatosis labialis • In men: pearly penile papules on the coronal sulcus
Pathologic entities	• Infections – Secondary syphilis with condylomata lata – *Molluscum contagiosum* • Diseases of the skin and mucosa – Intradermal nevi – Skin tags – Seborrheic keratoses • Cancer – Intraepithelial neoplasia

Note: This table does not include manifestations, which are listed above.

Specimen collection and laboratory diagnosis
Cervical cytology (Pap smear or Pap test)

- Two different methods can be used to screen for cervical cancer and its precursors: a glass slide fixed with Cytospray (conventional) or liquid-based cytology (LBC). Access to LBC is limited to only a small number of jurisdictions in Canada at present.
  - LBC for women with an ordinary risk of cervical cancer is more sensitive than the conventional glass-slide smear and produces a lower rate of unusable samples.[28]
- Regular cervical screening is important for all women who are, or have ever been, sexually active. Some North American guidelines recommend starting within 3 years of initiation of penetrative sexual activity,[29] but European guidelines recommend starting at 25 years of age.[30,31]
- Provincial and territorial guidelines for cervical cytology vary across Canada.

- Cervical Cancer Prevention Network guidelines recommend annual Pap smears until two sequential normal Pap smears are obtained, then every 3 years if normal in immunocompetent individuals.[32]
- **Immunocompromised persons, especially those who are HIV-positive, require special attention. Please refer to a local expert for optimal management.**
- Cervical cancer is more frequent in women who have not had cervical screening at regular intervals[24,25,33] and women who are HIV-positive.[34]
- Many women who develop cervical cancer have had inadequate cytology on previous smears.[35]
- The best specimen collection device is the extended-tip spatula combined with the Cytobrush.[36]
- Results are reported in some jurisdictions using Bethesda 2001 terminology,[37] but this varies by province and territory.

HPV typing

- A meta-analysis of the available literature concluded that HPV DNA testing is better than repeat cytology in women who have atypical squamous cells of undetermined significance (ASCUS) on Pap smears.[38] The Pan Canadian Forum on Cervical Screening has recommended HPV DNA testing for this indication.[39]
- Co-testing using LBC and HPV DNA testing is approved in the U.S. for primary screening, but no such recommendation exists in Canada.
- HPV typing is not useful for EGWs, which are most likely caused by low-risk non-oncogenic types,[2] or in women with LSILs or HSILs, because of the high prevalence of oncogenic types in such cases.[40]
- Access to HPV DNA tests in Canada is limited to a small number of jurisdictions at present.

Colposcopy

- Colposcopy should be performed for the following:
  - Clinically visible growths, warts or suspicious findings on the cervix.
  - Abnormal cervical screening test results, including the following:
    - Repeat ASCUS (especially if HPV detection test is positive)
    - ASCUS — cannot exclude high-grade lesion
    - LSILs
    - HSILs
    - Atypical glandular cells
    - Invasive carcinoma
  - Positive high-risk HPV detection twice in a 6–12 month period, even in the presence of normal cytology.
- Routine colposcopy for women with EGWs is not likely to be beneficial unless other criteria (see above) are present.[41]

Aceto-whitening or aceto-acid testing

- A solution of 5% acetic acid applied to the genital skin or the cervix for 1–3 minutes may lead to whitening of HPV-infected epithelium; however, this test has a high false-positive rate in both female and male patients.
- This test is never recommended for screening of external anogenital warts or subclinical lesions, even for partners of persons with an abnormal Pap smear or EGWs.
- This test should be reserved as an adjunct to colposcopy to increase the visibility of subclinical lesions.

Anoscopy

- Anoscopy should be considered in patients with anal warts.
- Anal cancer is being studied with anal Pap and viral testing as a screening method. Patients with positive results are then managed following clinical evaluation done by high-resolution anoscopy. This may be particularly important for HIV-positive patients.

Urethroscopy

- Urethroscopy can be considered for patients with extensive urethral warts not amenable to other forms of therapy.

Caution

Atypical and/or non-healing warts

- **Suspect neoplasia if any of the following are present:**
  - **Pigmented lesions**
  - **Bleeding**
  - **Persistent ulceration**
  - **Persistent pruritus**
  - **Recalcitrant lesions**
- **Patients with suspicious lesions may require a biopsy; refer to a colleague experienced in this area.**

Management

- No therapy guarantees eradication of HPV.
- Cell-mediated immunity will eradicate most HPV infections over time in teens and young adults.
- Warts often have a high persistence/recurrence rate, but more than 90% of patients with EGWs experience complete clearance within 2 years, with or without treatment. However, disappearance of warts is not synonymous with HPV eradication.
- Clearance of cervical lesions approaches 90–95%. Successful therapy for cervical abnormalities is often followed by clearance of HPV. HPV testing is being used to help detect residual high-grade disease and recurrent high-grade cervical lesions.[42]

Treatment

EGWs in males and females

- New lesions, with all available treatments, can occur at sites that may have been treated. They can also occur at different sites at a rate of 20–30%.[43]
- All treatments are associated with local skin reactions that can best be addressed by decreasing the intensity of the treatment.
- Rates of efficacy are difficult to determine because of a lack of uniformity in clinical trials.

Table 3. Patient-applied treatments

Treatment	Recurrence rate	Safety issues	Comments
Imiquimod *[A-I]* • Self-applied three times a week (with at least 1 day between applications) for up to 16 weeks • Should be washed off after 6–8 hours	• Recurrence rates are lower (10%) than with any other therapeutic modality[44]	• **Should *not* be used in pregnancy**	• Mechanism of action is through immune modulation
Podofilox/ podophyllotoxin 0.5% solution *[A-I]* • Applied to warts (but not the contiguous skin) every 12 hours for 3 consecutive days of each week (4 days off)[45] • Can be repeated for up to a maximum of 6 weeks only, with the total dose per day not to exceed 0.5 mL	• Recurrence rates are high (60%) • More efficacious, stable and associated with fewer side effects than podophyllin (see *Table 4*)	• **Should *not* be used in pregnancy** • **Should *not* be used for the treatment of cervical, meatal, vaginal or anal warts**	• For self-application under the direction of a physician • Available under two brand names in Canada: Wartec™ and Condyline™

Note:

There has been no study comparing these two treatment options.

Table 4. Office-based treatments

Treatment	Recurrence rate	Safety issues	Comments
Cryotherapy *[A-I]*[46-48] • Liquid nitrogen, carbon dioxide (dry ice or Histofreeze), or nitrous oxide using cryoprobes • Provide sufficient freezing with a rim of 1–2 mm to form around the lesion	• Good response rates	• Safe for use in pregnancy • Aggressive treatment of genital warts can leave scarring	• Destruction of the skin is usually limited to the epidermis
Podophyllin 10–25% *[A-I]* • Should be applied to the wart and not contiguous skin, and must be washed off in 1–4 hours • May be repeated once or twice a week at weekly intervals, the total dose not to exceed 1–2 mL per visit		• **Should *not* be used in pregnancy; fetal death has been reported** • **Should *not* be used for the treatment of cervical, meatal, vaginal or anal warts** • Frequent local reactions such as erythema, tissue edema, pain, burning, itching, tenderness or bullous reactions often reported • Systemic toxicity has also been reported	• Patient applied therapies are preferred over this treatment option • Should be used only if other therapies cannot be used • Should *never* be left to self-application
Bi- or trichloracetic acid *[A-I]*[47,48] • Repeated weekly for 6–8 weeks • 50–80% solutions in 70% alcohol are most effective • Does not need to be washed off		• Safe for use in pregnancy • Caustic and may produce blisters and ulcerations	• Healthy skin should be protected with petroleum jelly, 2% Xylocaine ointment or eutectic mixture of lidocaine and prilocaine cream
Electro-fulguration, CO_2 laser ablation, Excision[49]	• Good response rates	• Poor depth control may cause excess damage and scarring	• These treatment options are done for more extensive genital, perineal or anal warts

Note: Topical analgesia with lidocaine or eutectic mixture of lidocaine and prilocaine cream can be used for reduction of pain with office-based therapies.

Extensive, large or resistant external lesions, and internal lesions including vaginal, cervical, anal, urethral and meatal warts

- Patients should be referred to a colleague experienced in this area. CO_2 laser, trichloracetic acid, electroexcision, scissor excision and fulguration may require local or general anesthesia. Low rates of complications are expected if performed by an experienced physician.
- Patients with HIV infection often present with extensive anogenital warts with poor response to treatment.
- The following treatments are *not* recommended:
  - Interferon beta (Intron-A™)
  - Dinitrochlorobenzene sensitization
  - Cidofovir
  - Retinoic acid
  - Application immunotherapy with autogenous vaccines
  - 5% 5-fluorouracil cream

Male partners of women with abnormal Pap smears

- Since abnormal Pap smears most often represent the reactivation of an oncogenic latent strain, there is no clinical follow-up required for asymptomatic male partners. Previously, these men were subjected to aceto-whitening of the genital area and treatment for subclinical lesions. There are no data to support this *[D-III]*.[41]

Subclinical lesions

- Lesions may be visible only after examination or application of aceto-whitening. No specific management is recommended or necessary for subclinical lesions of the external anogenital skin, as neither recurrences of clinical warts nor transmission to partners is affected *[D-III]*.

Consideration for Other STIs

- See *Primary Care and Sexually Transmitted Infections* chapter.
- In patients with condylomata acuminata, an abnormal cervical smear and STI risk factors, obtain specimen(s) for the diagnosis of chlamydial and gonococcal infections.
- HIV testing and counselling are recommended (see *Human Immunodeficiency Virus Infections* chapter).
- Immunization against hepatitis B is recommended (see *Hepatitis B Virus Infections* chapter).
- Consider obtaining a blood sample for serologic testing for syphilis (see *Syphilis* chapter), especially in the presence of condylomata lata.

Reporting and Partner Notification

- HPV is not a reportable infection in Canada.
- "Standard" partner notification recommendations that apply for other STIs are not useful in reducing transmission of HPV.
- Patients should be encouraged to inform their sex partner(s) that they have or have had genital warts or an abnormal Pap smear, but there is no proof that this will lower the risk to the partner.
- Treatment or referral of asymptomatic partners is not indicated.[41]

Follow-up

- Once genital warts are healed, conduct routine follow-up of women with cervical screening, with or without HPV DNA testing, as recommended by provincial/territorial guidelines.
- Loss to follow-up treatment after abnormal cervical cytology is a significant issue, with rates as high as 40% in some jurisdictions.[50–52]

Special Considerations

Patients with HIV

- Patients with HIV infection require special care. Conjoint follow-up with an experienced colleague may be indicated.

Children and pregnant patients

- Refer to a colleague experienced in this area, since the psychological aspects and management can be difficult.
- **Consider the possibility of sexual abuse when genital warts are present in a child older than 18 months, and particularly in a child older than 2 years of age (see *Sexual Abuse in Peripubertal and Prepubertal Children* chapter).**
- Cesarean section is not recommended unless warts obstruct the birth canal.[41] Approximately 50% of cases of condyloma associated with pregnancy spontaneously regress in the first 3 months after delivery.