

Canadian Guidelines on Sexually Transmitted Infections

Human Papillomavirus (HPV) Infections Chapter

Revised:
December
2014



Public Health
Agency of Canada

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Canada

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Également disponible en français sous le titre :

Lignes directrices canadiennes sur les infections transmissibles sexuellement

– *Chapitre sur les infections au virus du papillome humain (VPH)*

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This publication can be made available in alternative formats upon request.

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Publication date: September 2014

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Cat.: HP40-1/2-2014E-PDF

ISBN: 978-1-100-25190-5

Pub.: 140315

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Health professionals with specialized expertise volunteered their time as external reviewers for this guideline chapter. The Agency and the Expert working group would like to thank those individuals for their valuable time and input.

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This document is intended to provide information to public health and clinical professionals and does not supersede any provincial/territorial legislative, regulatory, policy and practice requirements or professional guidelines that govern the practice of health professionals in their respective jurisdictions, whose recommendations may differ due to local epidemiology or context.

HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS

This chapter covers the prevention and management of human papillomavirus (HPV) infection, with particular attention to infections of the anogenital tract and their sequelae such as anogenital warts (AGWs), precancers and cancers.

Etiology

- More than 40 types of HPV are known to infect the moist mucosa of the anogenital tract, the oral cavity, and the oropharynx. Other types infect the skin.⁽¹⁾
- Persistent infection with one or more oncogenic, high-risk (HR) types may lead to precancerous or cancerous lesions of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and larynx.^(2,3) For more information, refer to *Appendix A: HPV groups, types and related cancer risk*.
- Infection with low-risk (LR) types such as 6 and 11 is associated with low or no cancer risk,⁽²⁾ but may lead to AGWs, low-grade squamous intraepithelial lesions (LSIL) of the cervix, and rare conditions such as recurrent respiratory papillomatosis (RRP).^(4,5)

Epidemiology

Transmission

- HPV is readily transmissible between opposite and same sex partners through receptive and penetrative vaginal, anal and oral sex, and non-penetrative sex (digital-vaginal sex and skin-to-skin contact).^(1,6)
- Vertical transmission is also possible, although mechanisms are not well understood.^(7,8)
- Infection with multiple types is common—particularly in those with AGWs.^(5,9-15)
- Infection with one HPV type does not appear to provide protection against infection with related HPV types.^(12,15)

Rates

- Globally, infections with HPV are common in both sexes.⁽¹⁶⁻²²⁾ Consequently, AGWs, and HPV-related precancers and cancers are significant public health problems.
- Prevalence in females is usually highest in those aged less than 25 years;⁽²³⁻²⁵⁾ prevalence in males is high at all ages.⁽²⁶⁾
- The estimated lifetime risk of infection is about 75%.⁽²⁷⁾
- In Canada, infections with HPV are also common, although prevalence may vary by subpopulation: meta-analysis suggests that HR HPV prevalence is higher in socially disadvantaged females such as those living in low income housing, inner city settings, or Aboriginal communities.⁽²⁸⁾

- In recent years, HPV frequency appears to have decreased in countries where HPV immunization programs for females have been introduced. For example,
 - in Australia and England, the prevalence of HR HPV types 16 and 18 decreased in young females;^(29,30)
 - in the U.S., the prevalence of LR and HR vaccine types 6, 11, 16 and 18 decreased in young females;⁽³¹⁾
 - in Australia, Denmark, England, Germany, New Zealand and Sweden, the incidence of AGWs in females decreased significantly following introduction of a quadrivalent vaccine,⁽³²⁻³⁷⁾ and
 - in Australia, the incidence of AGWs among males and the odds of cervical abnormalities in women also decreased.⁽³²⁾
- For more information, refer to *Appendix B: HPV incidence and prevalence*.

Risk Factors

Risk factors for infection with HPV

- Sexual behaviour:
 - the main determinant of infection,^(13,38) evidenced by high (41%) HPV type concordance between new sexual partners;⁽³⁹⁾
 - commencement of sexual activity itself (sexual debut),⁽⁴⁰⁾ acquisition of a new sexual partner,⁽³⁹⁾ higher number of recent sexual partners^(41,42) and higher number of lifetime sexual partners⁽⁴¹⁾ particularly significant.
- **Age less than 25 years (in females only)**, although all ages are affected.⁽²³⁻²⁵⁾
- **Co-infection with HIV:** associated with higher rates of cervical infection in HIV positive women,⁽¹⁾ and anal infection in HIV positive men who have sex with men (MSM)^(1,43)
- **Smoking:** associated with increased prevalence of HPV,⁽⁴⁴⁾ and the development of AGWs^(25,38)

Risk factors for anogenital warts

- **Same as for HPV infection**
- **PLUS**
- **Infection with LR HPV type 6 or 11**^(4,5)
- **Male gender**^(21,45)
- **Unprotected intercourse**⁽²⁵⁾
- **History of other sexually transmitted infections (STIs)**⁽²⁵⁾
- **Use of oral contraceptives**⁽²⁵⁾

Risk factors for HPV-related precancers

- **History of AGWs:** associated with an increased risk of cervical intraepithelial neoplasia (CIN) 2/3⁽⁴⁶⁾
- **Receptive anal intercourse:** associated with an increased risk of anal intraepithelial lesions (AIN) in HIV positive men⁽⁴⁷⁾
- **Co-infection with HIV:** associated with higher rates of CIN⁽¹⁾ and AIN^(1,43)
- **Smoking:** considered a co-factor in the development of CIN⁽¹⁾

Risk factors for HPV-related cancer

- **Persistent infection with HR HPV type:**
 - Type 16 linked to more than 1/2 of cervical cancer cases and type 18 to almost 1/5 of cases⁽⁴⁸⁾
 - Types 16, 18, 45, 31, 33, 52, 58 and 35 collectively linked to 9/10 of cervical cancers cases⁽⁴⁸⁾
 - Types 16 and 18 also linked to other cancers of the anogenital tract, oral cavity, and oropharynx⁽¹⁾
- **Infection by site:**
 - association between infection with HPV and almost all cervical cancers and anal cancers, 2/3 of vaginal cancers, 1/3 or more of penile cancers, and 1/3 or more of oropharyngeal squamous cell carcinomas⁽⁴⁹⁻⁵¹⁾
 - increasing association between HPV infection and oropharyngeal, including tonsillar, cancers^(52,53)
- **Co-infection with HIV:** associated with higher rates of cervical, anal, vulvar, vaginal and penile cancers^(1,54)—with anal cancer being particularly high among HIV positive MSM⁽⁵⁵⁾
- **Smoking:** considered a co-factor in the development of cervical cancer⁽¹⁾
- **History of HPV-related cervical, vulvar or anal cancer:** associated with an increased risk of a second, primary anogenital or head and neck cancer⁽⁵⁶⁻⁵⁸⁾
- **Other:**
 - Between 1994 and 2000, rates of HPV-associated anal cancer similar for women and men in the U.S. (slightly more than 2 per 100,000 in both women and men)⁽⁵⁵⁾
 - Oral contraceptive/cervical cancer relationship inconclusive⁽¹⁾

For more information concerning the epidemiology of HPV, refer to the **Epidemiology** section of the National Advisory Committee on Immunization (NACI) 2012 [Update on Human Papillomavirus \(HPV\) Vaccines](#).

Prevention

Immunization against HPV

Immunization is recommended for females and males of certain ages, whether or not they have previously been diagnosed with HPV-related disease. Refer to the [Canadian Immunization Guide](#) and *provincial/territorial immunization guidelines* (the webpage [Publicly Funded Immunization Programs in Canada—Routine Schedule for Infants and Children including Special Programs and Catch-up Programs](#) contains summary information about provincial/territorial immunization programs).

Male condom use

- Consistent male condom use is recommended for those with AGWs, having a partner with AGWs, or engaging in any sexual activity with new sexual partners because it may reduce the risk of:
 - cervical and vulvovaginal HPV infections in women,^(59,60)
 - anal HPV infections in men,⁽⁶¹⁾

- AGWs in men and women,⁽⁶²⁾ and
- CIN2, CIN 3, and invasive cervical cancer in women.⁽⁶²⁾

Cancer screening

- For information about cervical cancer screening, refer to the *Laboratory diagnosis of precancers and cancers* section.
- For information about anal cancer screening, refer to *Appendix E: Screening for anal cancer*.

Prevention counselling

(counselling for individuals with no visible lesions or other signs of HPV-related disease)

- Inform them that HPV is common and readily transmissible through penetrative and non-penetrative sexual activity; and that infected individuals may be asymptomatic.
- Provide them with information about risk factors (refer to the **Epidemiology** section), and risk reduction through immunization, consistent male condom use, cancer screening, regular self-examination of the anogenital area for wart-like lesions, and other behavioural change.
- Advise them to seek medical attention if wart-like lesions are found.

Manifestations and Major Sequelae

Infections with HPV

- **Signs and symptoms:** usually asymptomatic; normal Pap test (in women).⁽¹⁶⁾
- **Clearance**
 - usually clear without sequelae;⁽²⁵⁾
 - overall time to clearance of both HR and LR types may be similar in women and men (8 months in women⁽⁴²⁾ and 7 1/2 months in men⁽²⁶⁾);
 - HR types (particularly 16) tend to persist longer than LR types⁽⁶³⁾—especially in women.⁽⁶⁴⁾
- **Recurrence:** frequently reappear, whether due to re-activation of latent or undetectable virus, or re-infection.

Anogenital warts

- **Incubation Period:** 3 weeks to 8 months.⁽²⁵⁾
- **Appearance:**
 - multiple, asymmetrical, polymorphic exophytic fronds or growths on anogenital skin and/or mucous membranes that can vary in appearance from papular to cauliflower-like;
 - may fluctuate in size and number, or regress. For example, AGWs tend to increase in size and number during pregnancy, then to resolve spontaneously after delivery.⁽⁶⁵⁻⁶⁷⁾
- **Symptoms:** occasionally cause pruritus, local discharge and bleeding.⁽⁶⁸⁾
- **Clearance:** 10%-30% spontaneous clearance over 3 months;⁽⁶⁹⁾ median time to clearance 6 months.⁽⁷⁰⁾

- **Recurrence:** common.^(25,71) For information about recurrence following treatment, refer to the *Treatment of anogenital warts* section.
- **Sequelae:**
 - No effect on fertility.
 - Little impact on labour and delivery, unless they are obstructing the birth canal and may bleed excessively.⁽⁶⁵⁾
 - Psychosexual sequelae common, including fear of recurrence, transmission and development of cancer;⁽⁷²⁾ as well as depression, sexual dysfunction and disruption of long-term relationships.^(19,73)

Other LR HPV 6- and 11-associated lesions

- Refer to *Appendix C*.

HPV-related precancers and cancers

- For information about signs and symptoms, clearance rates and progression rates, refer to *Appendix D*.

Physical Examination, Specimen Collection and Laboratory Diagnosis

Physical examination and specimen collection

- Physical examination should include:
 - visual inspection of the external genitalia for wart-like lesions (the usual means of diagnosis of AGWs), precancers and cancers;
 - speculum examination of the vagina and cervix of women for wart-like lesions, precancers and cancers; and to obtain sample for Pap test;
 - digital anal examination for HIV positive individuals with perianal warts (recommended), given that the likelihood of intra-anal warts or neoplasia is high;
 - urethroscopy for those with urinary flow problems that may be the result of AGWs in the distal urethra or urethral meatus.
- Currently, there is no consensus about the use of anal Pap and high resolution anoscopy for screening those at increased risk of anal cancer (HIV positive and other immunosuppressed individuals; MSM; women with a history of anal intercourse and/or other HPV-related anogenital malignancies; and possibly, individuals with a history of AGWs).⁽⁵⁵⁾
- However, some experts suggest that those at increased risk may benefit from screening. For more information, refer to *Appendix E: Screening for anal cancer*.

Laboratory diagnosis of anogenital warts

- HPV nucleic acid testing is not recommended because results would not change management.

Laboratory diagnosis of precancers and cancers

- Two screening approaches to cervical cancer prevention currently exist:
 - Pap testing, which identifies HPV-related cytological abnormalities; and

- HPV nucleic acid testing, which identifies infection with HPV, whether or not cytological changes are evident. Check provincial/territorial screening guidelines for province/territory-specific screening recommendations.
- For information about anal cancer screening, refer to *Appendix E*.
- **Cervical cytology:**
 - Refer to the Canadian Task Force on Preventive Health Care 2013 [Recommendations on Screening for Cervical Cancer](#), and to provincial/territorial guidelines.
 - For information concerning provincial/territorial online resources about organized cancer screening programs, refer to [Population Based Cancer Screening Programs across Canada](#).
 - Note that provincial/territorial recommendations regarding the approach to testing, testing intervals, follow-up, and stop ages may differ from those of the task force.
 - For additional information about cervical cytology, refer to *Appendix F*.
 - Colposcopy referral recommendations vary by province or territory. Therefore, refer to provincial/territorial guidelines for information.
- **HPV nucleic acid testing:**
 - HPV nucleic acid testing is more sensitive than cytology but less specific,^(74,75) given that it can detect HPV DNA or RNA prior to the development of and in the presence of cytological abnormalities. It may therefore be a better predictor of potentially-serious HPV-related disease than cytology.
 - In the U.S., co-testing (concurrent use of HPV nucleic acid and Pap tests) for women aged 30 or more is approved.
 - In Canada, recommendations for testing can be found in the Canadian Task Force on Preventive Health Care 2013 [Recommendations on Screening for Cervical Cancer](#) and in province and territorial guidelines.
 - For a list of nucleic acid tests licensed for sale in Canada by Health Canada, refer to the [Medical Devices Active Licence Listing \(MDALL\)](#). Currently, the MDALL includes two DNA tests for HR HPV types in cervical samples, one DNA test for both HR and LR types, and two RNA tests for HR types. No nucleic acid tests for LR types only are licensed for sale in Canada.
 - For information about collection devices, and containers for storage and transport of specimens, refer to package inserts, or contact your local or provincial/territorial reference laboratory.
- **Histology:**
 - Colposcopy-directed cervical biopsy provides histological evidence to guide treatment.

Management

Management of subclinical lesions, anogenital warts, and cervical precancers, and cancers

- **Subclinical lesions:** treatment is not recommended.⁽⁶⁵⁾
- **AGWs:**
 - The goal is symptom relief.

- Foregoing treatment (an *expectant* approach) may be an acceptable option for some patients, given that AGWs may resolve spontaneously, and that treatment prevents neither transmission nor recurrence.
- Topical treatment of AGWs located in moist, occluded areas may be more effective than treatment of partly keratinized areas such as the penile shaft.^(65,76)
- Treatments may be patient- (self) or clinician-applied. The choice of treatment should be guided by:
 - patient preference,
 - availability of resources,
 - cost,
 - clinician’s experience,
 - size, shape, number and site of lesions,
 - convenience, and
 - potential adverse effects.⁽⁶⁵⁾
- Although self-applied treatments in the privacy of the home may be preferred by some, clinicians should consider whether patients can be expected to
 - comply with the regimen;
 - be able to identify and reach all of their lesions.
- **Cervical precancers and cancers:**
 - Refer to *Appendices G and H*.

Considerations for other sexually transmitted infections

- Testing for chlamydia, gonorrhea, HIV and syphilis may be considered, depending on risk factors and history of sexual contact. Refer to the [Primary Care and Sexually Transmitted Infections](#) chapter for information about STI screening.
- Immunization against hepatitis B is recommended. For more information, refer to the [Canadian Immunization Guide](#).
- For HIV positive individuals, consider shared follow-up with an experienced colleague, given:
 - increased risk of HPV infection, CIN, AIN, and HPV-related cancers;^(1,43,55,77)
 - counselling needs.

Considerations in children

- For information about immunization against HPV, refer to the [Canadian Immunization Guide](#) and to provincial/territorial immunization guidelines (for summary information about provincial/territorial immunization programs, refer to [Publicly Funded Immunization Programs in Canada – Routine Schedule for Infants and Children including special programs and catch-up programs](#)).
- **In children aged over 18 months (and particularly aged over 2 years) who have AGWs, consider:**
 - **sexual abuse rather than vertical transmission as a possible cause;** refer to the [Sexual Abuse in Peripubertal and Prepubertal Children](#) chapter;
 - referral to a colleague with expertise in this area since management (which includes management of the psychological aspects) can be challenging;

- treatment-specific considerations and contraindications described in the **Treatment** section.
- Once lesions have cleared, further treatment is not needed.

Considerations in pregnant and breastfeeding women

- Collect specimen for Pap testing at the first antenatal visit if Pap testing is due or overdue. For more information, refer to the Canadian Task Force on Preventative Health Care 2013 [Recommendations on Screening for Cervical Cancer](#).
- Refer those requiring follow-up to a colposcopist experienced in assessing the pregnant cervix.⁽⁷⁷⁾
- Advise women with AGWs that:
 - All topical treatments except trichloroacetic acid (TCA) are contraindicated for use in pregnant and breastfeeding women. For more information, refer to the **Treatment** section.
 - Removal may be considered. However, complete resolution may not occur until after delivery.⁽⁶⁵⁾
 - The presence of AGWs is not an indication for caesarean section unless they are obstructing the birth canal and may bleed excessively.⁽⁶⁵⁾

Considerations in those who are immunocompromised

- Use imiquimod⁽⁷⁸⁻⁸⁰⁾ with caution.
- The use of sinecatechins is contraindicated for those receiving immunosuppressive therapy.⁽⁸¹⁾

Counselling

- Inform those with abnormal cervical Pap test results, positive HPV tests and/or AGWs that:
 - Determining when and from whom their infection was acquired is virtually impossible because HPV is common, readily transmissible through penetrative and non-penetrative sexual activity, and has a long incubation period;⁽²⁵⁾ infected individuals may be asymptomatic and undiagnosed (testing is not routine); and sequelae can reappear long after the initial infection.
 - Infection with HPV rarely leads to cervical cancer because:
 - most infections appear to resolve spontaneously without treatment;⁽²⁵⁾ and
 - most cervical cancer precursors can be successfully treated.⁽⁸²⁾
 - Following treatment for AGWs or precancers, the risk of new or reactivated HPV infections, and related anogenital disease is linked to
 - behavioural factors—particularly sexual behaviours, smoking, and possibly, the use of oral contraceptives;
 - HPV types;
 - medical history of AGWs, HPV-related cancer, and/or HIV infection;
 - immunization status.
 - The risk of new infections may be reduced through immunization, consistent male condom use, and other behavioural change; while the risk of advanced anogenital disease may be reduced through cancer screening.

- Discussion of risk reduction strategies with sexual partners is recommended.
- HPV nucleic acid testing is not recommended because results would not change management.
- Unlike cervical cancer precursor lesions, AGWs may be difficult to treat and often recur following treatment (for information about the efficacy of AGWs treatments and recurrence, refer to the **Treatment** section).
- Medical follow-up for partners is recommended only for those who find wart-like lesions on self-examination, or who might benefit from screening for other STIs.
- Provide sexual partners of those with AGWs or precancers with information about HPV epidemiology, and inform them that:
 - Risk can be reduced through immunization, consistent male condom use, cancer screening, regular self-examination of the genital area for wart-like lesions, and other behavioural change;
 - Medical follow-up for partners is recommended only for those who find wart-like lesions on self-examination or who might benefit from screening for other STIs.

Treatment

Treatment of anogenital warts

Treatment-specific considerations and contraindications

- **Topical treatments**, including imiquimod, podofilox/podophyllotoxin, podophyllin, sinecatechins, and trichloroacetic acid (TCA)
 - **For external use only, under the direction of a physician:**
 - All listed topical treatments except TCA.^(78-81,83-85)
 - Avoid contact with mucosal tissue, eyes, tongue, lips, broken skin and surrounding, healthy skin. For information about how to protect surrounding, healthy skin, refer to product monographs.
 - Caution patients to refrain from sexual activity while undergoing treatment.
 - **May cause skin reactions** ranging from itching, tenderness and erythema, to ulceration:
 - For information about neutralizing agents, refer to product monographs.
 - Also consider reducing treatment frequency and/or intensity.
 - **For pain reduction**, consider use of a topical eutectic mixture of lidocaine and prilocaine cream, or if needed, injectable lidocaine solution, prior to treatment.
 - **May cause systemic reactions:** all listed topical treatments except sinecatechins and TCA
 - **May need to be combined with clinician-applied therapies, if AGWs persist post-treatment**^(86,87)
 - **Contraindications:**
 - **Not recommended for pregnant and breastfeeding women:** all listed topical treatments except TCA^(78-81,83-85,88)
 - **Not recommended for children and adolescents less than 18 years:** imiquimod and sinecatechins⁽⁷⁸⁻⁸¹⁾

- **Not recommended for children and adolescents less than 12 years:** podofilox/podophyllotoxin (Wartec) and podophyllin^(84,88)
- **Not recommended for diabetics and those with poor circulation:** podofilox/podophyllotoxin and podophyllin^(83,88)
- **Contraindicated for those receiving immunosuppressive therapy and those with allergies to green tea extract:** sinecatechins⁽⁸¹⁾
- For additional information, refer to product monographs, and to chapter 6 of the [Canadian Consensus Guidelines on Human Papillomavirus](#).
- **Ablative Treatments**
 - **For pain reduction**, consider:
 - a topical eutectic mixture of lidocaine and prilocaine cream prior to treatment for external warts, or injectable lidocaine solution;
 - local analgesia or rarely, general anaesthesia, prior to treatment for internal cervical, intra-anal, intravaginal, meatal and oral warts.
 - When affected area is extensive, consider CO2 laser and surgical techniques. However, poor laser depth control may cause scarring.⁽⁸⁹⁾

Patient-applied topical treatments

- In addition to the topical treatments listed alphabetically in *Table 1*, over-the-counter, self-applied “cryotherapy” kits are also available.
- For information about treatment-specific considerations and contraindications, refer to the [Treatment-specific considerations and contraindications](#) section.

Table 1: Patient-applied topical treatments for penile, perianal, perineal, pubic, scrotal, vulvar, inguinal fold, buttock and buttock fold warts

Treatment (external use only)	Clearance	Recurrence	Comments
Imiquimod 3.75% cream [A-I] <ul style="list-style-type: none"> Apply daily at bedtime for up to 8 weeks Wash off after approximately 8 hours^(78,80) 	Females 36%; Males 16% ^(78,80)	Both sexes 17% ⁽⁷⁸⁾	<ul style="list-style-type: none"> Immune modulator Causes fewer local skin reactions than imiquimod 5% cream⁽⁹⁰⁾ Best outcomes in women: perianal, perineal, vulvar and inguinal AGWs Best outcomes in men: glans penis, scrotum, inguinal and penile AGWs⁽⁷⁸⁻⁸⁰⁾
Imiquimod 5% cream [A-I] <ul style="list-style-type: none"> Apply 3 times a week at bedtime, with 1–2 days between treatments, for up to 16 weeks Wash off after 6-10 hours, or earlier if local skin reaction occurs⁽⁷⁹⁾ 	Females 72%; Males 33% ⁽⁷⁹⁾	Females 19%; Males 6% ⁽⁷⁹⁾	<ul style="list-style-type: none"> Immune modulator Long treatment schedule may decrease adherence Comparison of imiquimod 3.75% and 5% efficacy rates precluded by differences in study designs
Podophyllotoxin/ Podofilox 0.5% soln. [A-I] <ul style="list-style-type: none"> Wash and dry affected area, and protect surrounding skin with petroleum jelly Apply treatment with a cotton swab q12h for 3 days (followed by 4 days without treatment) for up to 4 weeks Need not be washed off Daily dose: <0.5 ml to an area ≤10cm²^(65,83,84) 	Both sexes (mostly males) 53%-78% ^(76,91-94)	Both sexes (mostly males) 17%-79% ^(76,91,93,95)	<ul style="list-style-type: none"> Safer, more effective and cost effective than physician-applied podophyllin resin^(4,91,95,96) Use with caution near the urethral meatus. Consider alternative treatment if response incomplete after 4 cycles
Sinecatechins 10% ointment [A1] <ul style="list-style-type: none"> Apply 0.5 cm strand tid for up to 16 weeks Daily dose: ≤ 250 mg Need not be washed off⁽⁸¹⁾ 	Females 65%; Males 48% ⁽⁹⁷⁾	Both sexes 6.5% ⁽⁹⁷⁾	<ul style="list-style-type: none"> May be more effective on keratinized AGWs than other topical treatments⁽⁹⁷⁾

Clinician-applied topical and ablative treatments for external anogenital warts

- For information about treatment-specific considerations and contraindications, refer to the [Treatment-specific considerations and contraindications](#) section.

Table 2. Clinician-applied topical and ablative treatments for penile, perineal, perianal, pubic, scrotal, vulvar, inguinal fold, buttock and buttock fold warts

Treatment	Clearance	Recurrence	Comments
<p>Podophyllin 25%* [A1]</p> <ul style="list-style-type: none"> Wash and dry affected area, and protect surrounding skin with petroleum jelly. Apply 1-2 ml weekly for up to 6 weeks Allow to air dry Wash off first application in 1 hour; and if no adverse reaction, subsequent applications in 4-6 hours^(88,98) 	<ul style="list-style-type: none"> Both sexes 19%— 79%^(95,96,99-101) 	<ul style="list-style-type: none"> Both sexes 17%— 74%^(98,100,101) 	<ul style="list-style-type: none"> For use only in the absence of other treatment options, given concerns about local and systemic safety, and low efficacy Should never be self-applied Patient-applied treatments preferred
<p>Trichloroacetic acid 50%—90% soln. in 70% alcohol [A-I]</p> <ul style="list-style-type: none"> Protect healthy skin with petroleum jelly or talc Consider local analgesia with a topical eutectic mixture of lidocaine and prilocaine cream, or with injectable lidocaine 2% Can be neutralized with liquid soap, sodium bicarbonate, or talc, if necessary Apply weekly for 6–8 weeks Does not need to be washed off⁽¹⁰²⁾ 	<ul style="list-style-type: none"> Both sexes: 70%— 81%^(103,104) 	<ul style="list-style-type: none"> Both sexes: 36%⁽¹⁰⁴⁾ 	<ul style="list-style-type: none"> Safe for use in pregnancy More suitable for small or papular warts than larger or keratinised lesions Caustic; may produce blisters and ulceration
<p>Cryotherapy [A-I]</p> <ul style="list-style-type: none"> Apply liquid nitrogen, carbon dioxide (dry ice or over-the-counter product), or nitrous oxide using cryoprobes to create a 1–2 mm halo around the lesion (1-2 freeze-thaw cycles) weekly for up to 4 weeks⁽¹⁰³⁻¹⁰⁵⁾ 	<ul style="list-style-type: none"> Both sexes: 79%– 88%^(101,103,104) 	<ul style="list-style-type: none"> Both sexes: 24%– 40%^(101,104) 	<ul style="list-style-type: none"> More acceptable than electrocautery⁽¹⁰⁵⁾ Destruction of the skin usually limited to the epidermis or squamous mucous membranes, but can result in scarring if treatment aggressive
<p>Surgical treatments</p> <ul style="list-style-type: none"> CO2 laser vaporization Electrosurgical treatments (electrosurgical coagulation, electrofulguration, or infrared coagulation) Surgical excision (scalpel, scissors or loop) 	<ul style="list-style-type: none"> CO2 laser: 67%–100%, with some variation by gender and number of treatments⁽¹⁰⁶⁻¹¹⁰⁾ Electrosurgery 94%⁽¹⁰¹⁾ Surgical excision: 89%–93%^(100,111) 	<ul style="list-style-type: none"> CO2 laser: 7%–25%, with some variation by gender⁽¹⁰⁷⁻¹¹⁰⁾ Electrosurgery 23%⁽¹⁰¹⁾ Surgical excision: 18%–19%^(100,111) 	<ul style="list-style-type: none"> CO2 laser: not a first line therapy but may be considered for more extensive genital, perineal or anal warts Damage and scarring if depth control poor

* Podophyllin 25% is approved for sale in Canada. The percentage of podophyllin in studies of AGWs clearance and recurrence, however, ranged from 10%-25%.

Clinician-applied topical and ablative treatments for internal anogenital warts

- TCA, cryotherapy, electrosurgery, and surgical excision using scissors or scalpel may be used for the treatment of cervical, intra-anal, intravaginal, and meatal warts.⁽¹¹²⁾
- They may also be used for the treatment of oral warts, although few evaluations of such treatments have been reported in the scientific literature.
- Additionally, CO₂ laser vaporization can be used for intra-anal warts. However, it can cause scarring, and vaginal or rectal perforation; therefore, special training is needed.⁽¹⁰²⁾
- Individuals with intra-urethral warts should be referred to an urologist.
- The following are not recommended: interferon beta (Intron-A), dinitrochlorobenzene sensitization, 1%-2% cidofovir ointment, retinoic acid, immunotherapy with autogenous vaccines, and 5% 5-fluorouracil cream.

Treatment of cervical precancers and cancers

- Refer to *Appendix H*.

Reporting and Partner Notification

- Infection with HPV is not a notifiable condition in Canada.
- Partner notification is not required but can be helpful in encouraging risk reduction practices; including behavioural change and immunization (refer to *Counselling* sections).
- Additionally, individuals with AGWs should consider discussing preventive measures such as immunization, consistent male condom use, screening, and self-examination with new partners.

Follow-up

- Immunization is recommended for females and males of certain ages, whether or not they have previously been diagnosed with HPV-related disease. Refer to the [Canadian Immunization Guide](#) and provincial/territorial immunization guidelines (the webpage [Publicly Funded Immunization Programs in Canada—Routine Schedule for Infants and Children including Special Programs and Catch-up Programs](#) contains summary information about provincial/territorial immunization programs).
- Refer to provincial/territorial cervical cancer screening guidelines for guidance about follow-up to abnormal cervical Pap tests.
- Refer to local practice or consensus guidelines for guidance about follow-up to abnormal anal Pap tests.
- Medical follow-up for partners is recommended only for those who find wart-like lesions in the anogenital area, or who might benefit from screening for other STIs.

Appendices

Appendix A: HPV groups, types and related cancer risk ^(2,113)

Group	Carcinogenicity	HPV type	Comments	Clinical Conditions
1	Carcinogenic	16 (alpha type)	<ul style="list-style-type: none"> • Most potent • Most common • Sufficient evidence in humans for cancer at several sites • Strong mechanistic evidence of carcinogenicity 	<ul style="list-style-type: none"> • Cancer of the cervix vulva, vagina, penis, anus, oral cavity and oropharynx (including tonsils)
		18 (alpha type)	<ul style="list-style-type: none"> • Sufficient evidence in humans for cervical cancer • Positive association with cancer at several other sites • Strong mechanistic evidence of carcinogenicity 	<ul style="list-style-type: none"> • Cancer of the cervix • Positive association with cancer of the vulva, penis, anus, oral cavity and larynx
		33 (alpha type)	<ul style="list-style-type: none"> • Sufficient evidence in humans for cervical cancer • Moderate mechanistic evidence of carcinogenicity • Positive association with cancer at other sites 	<ul style="list-style-type: none"> • Cancer of the cervix • Positive association with cancer of the vulva and anus
		31, 35, 39, 45, 51, 52, 56, 58, 59 (alpha types)	<ul style="list-style-type: none"> • Sufficient evidence in humans for cervical cancer • Positive (all types except 31 and 59) to moderate (type 31 only) mechanistic evidence of carcinogenicity for all but type 59 	<ul style="list-style-type: none"> • Cancer of the cervix
2A	Probably carcinogenic	68 (alpha type)	<ul style="list-style-type: none"> • Limited evidence in humans • Positive mechanistic evidence of carcinogenicity • Positive association with cancer of the cervix 	<ul style="list-style-type: none"> • Positive association with cancer of the cervix
2B	Possibly carcinogenic	26, 53, 66, 67, 70, 73, 82 (alpha types)	<ul style="list-style-type: none"> • Limited evidence in humans • Positive mechanistic evidence of carcinogenicity (types 53, 66 and 82) • Positive association with cancer of the cervix 	<ul style="list-style-type: none"> • Positive association with cancer of the cervix
		30, 34, 69, 85, 97 (alpha types)	<ul style="list-style-type: none"> • Inadequate evidence in humans • Potentially carcinogenic, based on phylogenetic similarity to other HPV types 	

Group	Carcinogenicity	HPV type	Comments	Clinical Conditions
		5, 8 (beta HPV types)	<ul style="list-style-type: none"> Limited evidence of carcinogenicity 	<ul style="list-style-type: none"> Skin cancer in patients with epidermodysplasia verruciformis
3	Not classifiable (that is, evidence of carcinogenicity is inadequate in humans and usually, inadequate or limited in animals as well; or agent does not fall in any other category)	6, 11 (alpha types)	<ul style="list-style-type: none"> Inadequate evidence of carcinogenicity Little or no mechanistic evidence of carcinogenicity 	<ul style="list-style-type: none"> Cancer of the larynx
		Other beta and gamma types	<ul style="list-style-type: none"> Inadequate evidence in humans 	<ul style="list-style-type: none"> Skin cancer

Appendix B: HPV incidence and prevalence

- Globally, infections with HPV are common in both sexes.
 - HR types 16, 18, 31, 52, and 58 are consistently among the 10 most common types found in women with normal cytology (normal Pap).^(16,22)
 - LR types are also common.⁽¹⁷⁻²¹⁾
- Prevalence in females is usually highest in those aged less than 25 years;⁽²³⁻²⁵⁾ prevalence in males is high at all ages (approximately 60%, according to the HPV in men [HIM] study).⁽²⁶⁾
- The estimated lifetime risk of HPV infection in men and women aged 15-49 years is about 75%, based on U.S. data.⁽²⁷⁾
- Consequently, sequelae such as AGWs, and HPV-related precancers and cancers are significant public health problems. For example, prior to the introduction of a quadrivalent vaccine against HPV:
 - An HPV vaccine trial placebo group that included women from 16 countries found that the incidence of AGWs was 3.4% (0.87 cases per 100 person years [PY]) at risk.⁽¹⁸⁾
 - In the U.S., somewhat higher rates (from 170 per 100,000 PY in 2000⁽¹⁹⁾ to 205 per 100,000 PY in 2001⁽²⁰⁾) were reported.
 - 5.6% of sexually active American adults aged 18–59.⁽¹⁷⁾
 - 10.6% of women aged 18-45 from 4 Nordic countries (Denmark, Iceland, Norway and Sweden) reported having ever been diagnosed with AGWs.
- Infection with HPV is also common in Canada. For example,
 - the prevalence of HPV in heterosexual men attending a B.C. sexual health clinic was found to be 69.8%;⁽²²⁾
 - AGWs (resulting from infection with HPV 6 or 11) are also common:
 - The incidence of AGWs in a British Columbia study was 121 per 100,000 in women and 131 per 100,000 in men (2006).⁽²¹⁾
 - The incidence in a Manitoba study was 120 per 100,000 in women and 154 per 100,000 in men (2004).⁽⁴⁵⁾
 - The incidence and prevalence of AGWs in B.C had increased over the 8 year study period.⁽²¹⁾
- However, HPV prevalence in Canada may vary by subpopulation; meta-analysis of Canadian oncogenic (HR) HPV prevalence studies showed that prevalence in females ranged from 14.1%–46.9%; and was highest in those aged less than 20 years and living in low income inner city settings and Aboriginal communities.⁽²⁸⁾

Appendix C: Other LR HPV 6- and 11-associated lesions

- Low grade squamous intraepithelial lesions (LSIL).^(4,5)
- Rare conditions such as:
 - conjunctival, nasal and laryngeal warts;⁽⁶⁶⁾
 - high grade disease of the vulva, penis or perianal area previously known as Bowenoid papulosis (elevated lesions with verrucous surfaces, with or without keratinization and/or brown-red pigmentation or cancer—possibly due to co-infection with HR types);^(114,115)
 - Buschke-Lowenstein tumours (giant condylomata acuminata of the vulva, penis or anus, that may also proceed to cancer);^(1,116)
 - carcinoma of the larynx;^(1,116)
 - adult recurrent respiratory papillomatosis (RRP);⁽⁷¹⁾ and
 - juvenile recurrent respiratory papillomatosis (juvenile RRP or JoRRP), which has an incidence of 0.5–4.3 cases per 100,000 births;^(117,118) results from vertical mother-to-child transmission before or during delivery⁽¹¹⁸⁾ (risk is higher when mothers have a history of AGWs);⁽¹¹⁹⁾ and may resolve spontaneously or recur following treatment. Diagnosis before age 3 indicates more aggressive disease, is more closely linked to HPV 11 than to HPV 6,⁽¹²⁰⁾ and occasionally leads to death.⁽¹¹⁷⁾

Appendix D: Manifestations

- **Signs and symptoms**
 - Cervical precancers and cancers cause little or no discomfort—hence the need for screening.
 - Vaginal precancers and cancers are usually asymptomatic but may cause bleeding.
 - Vulvar precancerous lesions may cause itching, burning and/or pigment changes.
 - Cancerous lesions may bleed and/or be painful.
- **Clearance**
 - within 12 months, 70% of untreated CIN 1 and 54% of CIN 2 lesions ⁽¹²¹⁾
- **Progression of untreated precancerous cervical lesions**
 - 57% of CIN 1 lesions regress, 32% persist, 11% progress to carcinoma *in situ*, and 1% progress to invasive cervical cancer;
 - 43% of CIN 2 lesions regress; 35% persist; 22% progress to carcinoma *in situ*; and 5% progress to invasive cervical cancer.
 - 32% of CIN 3 lesions regress, less than 56% persist; and more than 12% progress to invasive cancer;⁽¹²²⁾
 - Progression of untreated or inadequately treated CIN 3 to invasive cancer may take from 0.3 to 45.0 years (median 27.1 years).⁽¹²³⁾
- **Progression of untreated precancerous anal lesions**
 - Less is known about the natural history of anal intraepithelial lesions and other HPV-related precancers than about cervical intraepithelial lesions, although high-grade anal lesions are known to be precursors of squamous cell carcinoma of the anus.⁽¹²⁴⁾
- **Differential diagnosis of AGWs**
 - Consider the following (and confirm by biopsy if diagnosis is uncertain):
 - non-pathological variations in sebaceous glands of both sexes (for example, Fordyce spots and Tyson's glands); vestibular papillae or micropapillomatosis labialis (in women); and pearly penile papules on the coronal sulcus (in men);⁽⁶⁸⁾
 - pathological entities caused by non-infectious diseases of the skin and mucosa, such as intradermal nevi; lichen planus; skin tags or acrochorda; seborrheic keratosis after the age of 35; and cylindroma;
 - pathological entities caused by infectious agents, such as Buschke-Lowenstein tumours; “water warts” of molluscum contagiosum; condylomata lata of secondary syphilis; and intraepithelial neoplasia.

Appendix E: Screening for anal cancer

- Population-based studies demonstrating the relationship between high grade AIN and anal cancer are lacking, as are studies demonstrating that treatment of high grade AIN prevents anal cancer.⁽⁵⁵⁾
- One study of HIV positive MSM found that anal Pap testing may be cost-effective.⁽¹²⁵⁾
- Currently, there is no consensus about the use of anal Pap and high resolution anoscopy for screening those at increased risk of anal cancer (HIV positive and other immunosuppressed individuals; MSM; women with a history of anal intercourse and/or other HPV-related anogenital malignancies; and possibly, individuals with a history of AGWs).⁽⁵⁵⁾
- However, expert opinion suggests that those at increased risk may benefit from screening.^(55,126,127)
- More studies—particularly, studies in the Canadian context—are needed before general recommendations for screening can be made.
- Until general recommendations are developed, anal Pap testing should be guided by local practice or consensus; and is dependent on the local availability of laboratory professionals with training and/or experience in reading anal cytology.
- Patients with positive results should be evaluated further using high-resolution anoscopy.⁽¹²⁸⁾

Appendix F: Additional information about cervical cytology

- Either the conventional or the liquid-based approach to specimen collection for Pap can be used: sensitivity does not differ significantly.⁽¹²⁹⁾
- However, the liquid-based approach allows sample residuals to be tested for HPV.
- The collection device should allow for adequate sampling from both the endocervix and exocervix.⁽¹³⁰⁾ The use of an endocervical brush or broom is contraindicated in pregnancy.
- Finding a squamous cell intraepithelial lesion usually indicates infection with HPV.
- Lesions are classified according to the Bethesda system as:
 - ASC-US, which indicates atypical squamous cells of undetermined significance, and the need for repeat Pap or HPV nucleic acid testing to clarify;
 - ASC-H, which indicates atypical squamous cells – cannot exclude HSIL;
 - LSIL, which indicates low-grade squamous intraepithelial lesion/mild dysplasia or CIN1;
 - HSIL, which indicates moderate or severe dysplasia/CIN2 or 3, or carcinoma *in situ*;
 - Invasive carcinoma.⁽¹³¹⁾
- Glandular lesions are similarly classified as:
 - Atypical glandular cells (AGC),
 - Adenocarcinoma *in situ* (AIS), and
 - Adenocarcinoma.
- AGCs require careful follow-up as 56% are associated with significant precancerous and cancerous conditions.⁽¹³²⁾
- Referral to a colposcopist for further investigation, including biopsy to obtain a sample for histological examination, is indicated when Pap, or Pap plus HPV nucleic acid testing, shows:
 - persistent ASC-US,
 - ASC-US in the presence of HR HPV type,
 - ASC-H,
 - persistent LSIL,
 - HSIL,
 - AGC,
 - AIS, or
 - invasive cancer.⁽¹³³⁾
- Referral to a colposcopist is also recommended for women whose HPV tests are positive two years in a row.

Appendix G: Management of cervical precancers and cancers

- Cytological indications for colposcopy are listed in Appendix F: Additional information about cervical cytology.
- Other indications for referral and biopsy include:
 - non-response to treatment,
 - abnormal pigmentation,
 - bleeding,
 - persistent itching or ulceration, and
 - lesion persistence or recurrence.
- Colposcopists may apply a solution of 5% acetic acid to genital mucosa (acetic acid whitening/acetowhitening) in order to visualize subclinical lesions of the cervix. This technique is not specific for HPV,⁽⁶⁵⁾ and has a high false-positive rate in both females and males. Hence, it is not recommended for visualizing AGWs and subclinical lesions in primary care settings, or for screening of asymptomatic partners of women with AGWs or abnormal cervical cytology.
- For guidance concerning the management of cytological abnormalities, refer to the Society of Obstetricians and Gynaecologists of Canada clinical practice guideline entitled [Colposcopic Management of Abnormal Cytology and Histology](#).
- AGWs are not an indication for colposcopy. Although Li et al. found a high prevalence of CIN2 and 3 in women with AGWs,⁽⁴⁶⁾ such women are likely to benefit from colposcopy only if Pap testing has already revealed cervical abnormalities.

Appendix H: Treatment of cervical precancers and cancers

- Treatment of precursor lesions greater than CIN 1 and of cervical and other HPV-related cancers is beyond the scope of these guidelines. Refer to provincial/territorial guidelines.
- No therapy guarantees the eradication of HPV.
- However, Chao et al. found that almost 90% of women treated for CIN 2/3 with conization had no residual or recurrent disease in the 3 years following treatment. Moreover, HPV testing was helpful in detecting residual high-grade disease and predicting risk of recurrence.⁽⁸²⁾

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