

United Kingdom National Guideline on the Management of Ano-genital Warts, 2007

Clinical Effectiveness Group (British Association for Sexual Health and HIV)

Scope and purpose

The main objective is to reduce the number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI, or undergoing investigation for possible infection.

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of ano-genital warts, covering the management of the initial presentation, as well as how to prevent transmission and future infection.

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in departments offering level 3 care in STI management (see national strategy⁽²⁾) within the United Kingdom. However, the principles of the recommendations should be adopted across all levels (levels 1 and 2 may need to develop, where appropriate, local care pathways).

This guideline was compiled by members of the BASHH HPV Special Interest Group without patient input.

Aetiology

Ano-genital warts are caused by the human papillomavirus (HPV) of which over 100 genotypes have been identified. The mode of transmission is most often by sexual contact but HPV may be transmitted perinatally and genital lesions resulting from transfer of infection from hand warts have been reported in children. There is no good evidence of transmission from fomites. Most ano-genital warts are benign and caused by HPV types 6 and 11. Some lesions may contain oncogenic types associated with genital tract dysplasia and cancers. Ano-genital warts are the 'tip of the iceberg' of genital infection with HPV, for example in the USA it has been estimated that there is an annual incidence of 1% of the adult population but many more people without warts have subclinical disease or latent infection⁽¹⁾.

Clinical features

Symptoms

In 2005 just over 80,000 new diagnoses of ano-genital warts were made in genitourinary (GU) medicine clinics in the United Kingdom⁽²⁾. Although the large majority of these result in little physical discomfort, they may be disfiguring and psychologically distressing⁽³⁾. Ano-genital warts may be associated with irritation and soreness especially around the anus. Symptoms of distortion of urine flow, or bleeding from the urethra or anus, may indicate internal lesions.

Signs

Warts are benign epithelial skin tumours:

- HPV is a multifocal infection of the ano-genital skin⁽⁴⁾ lesions being most common at the site of trauma at sexual intercourse, but may occur at any site⁽⁵⁾.
- Perianal lesions are common in both sexes, but are seen more commonly in homosexual men⁽⁵⁾.
- Warts in the anal canal are associated with penetrative anal sex^(5,6), and may indicate the need for samples to be taken from the ano-rectal region for other STIs, e.g. *N. gonorrhoeae* or *C. trachomatis*.
- Occult lesions may be seen on the vagina, cervix, urethral meatus, and anal canal⁽⁵⁾.
- Extragenital lesions may be seen on the oral cavity, larynx, conjunctivae, and nasal cavity.

Clinical appearances of exophytic warts:

- Warts may be single or multiple.
- Those on the warm, moist, non-hair bearing skin tend to be soft and non-keratinised and those on the dry hairy skin firm and keratinised.
- Lesions may be broad based or pedunculated and some are pigmented.

Diagnosis

- Naked eye examination in most cases
- If in doubt, or if the lesion is atypical or pigmented, suggesting possible intraepithelial neoplasia, biopsy under local anaesthetic for histology should be performed prior to any therapeutic intervention. This may be aided by the use of a colposcope.

Assessment of lesions

- Examine the external ano-genital and surrounding skin under good illumination
- Females, vaginal speculum examination
- Both sexes, proctoscopy may be indicated if history of anal receptive sex, or following clearance of perianal warts. Meatoscopy and proctoscopy should be performed if there is a history of distortion of urine flow or bleeding from the urethra or anus respectively. Occasionally urethroscopy is indicated for more proximal warts.
- Classify warts as to morphology
- Recording of lesions on genital maps at each visit is useful, providing a visual record of approximate number, distribution, and response to treatment
- Extragenital sites (e.g. oral cavity) examined if clinically indicated.

Management

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe. General advice

- Patients should be given a detailed explanation of their condition with particular emphasis on the long term implications for the health of themselves and their partners. This should be reinforced by giving them clear and accurate written information.
- Although data are conflicting, condoms have been shown to protect against the acquisition of HPV infection and genital warts⁽⁷⁻⁹⁾ and may also have a therapeutic effect when both partners are infected, possibly by preventing continued re-exposure to the virus.⁽¹⁰⁻¹²⁾ Considering current data, condom usage may prove beneficial and their use advisable, particularly in new relationships. (IIIb; B)

- Latex condoms may be weakened if in contact with imiquimod
- For some patients the psychological impact of warts is the worst aspect of the disease⁽³⁾. Where psychological distress is apparent, referral for counselling may be appropriate.
- There are data suggesting that smokers may respond less well to treatment than non-smokers. ^(13,14)

Further investigations

Many patients will have other concurrent sexually transmitted infections (STI). Therefore, an appropriate screen for STI is recommended⁽¹⁵⁾.
(See Sexually Transmitted Infections: UK National Screening and Testing Guidelines http://www.bashh.org/guidelines/2006/sti_screening_guidelines)

Subclinical lesions

Subclinical lesions of the external ano-genital skin are those not seen by the naked eye, but detectable by soaking the skin with 5% acetic acid and examining with magnification (e.g. a colposcope). These lesions are usually asymptomatic, but may cause irritation and inflammation of the skin- for example, atypical balanoposthitis⁽¹⁶⁾ or vulvitis⁽¹⁷⁾.

Problems associated with the identification of such lesions :

- Many aceto-white lesions are not caused by HPV⁽¹⁸⁾
- Histological changes are not specific for HPV infection⁽¹⁹⁾
- HPV detection is not routinely available.

Treatment of these lesions has not been shown to:

- affect the course of disease⁽²⁰⁾ in patients or their partners⁽⁷⁾

For the above reasons and the fact that identification may cause unnecessary anxiety, it is not recommended that these lesions are sought unless there is a clinical indication (IIb, B)

Treatment

Treatment choice depends on the morphology, number, and distribution of warts and patient preference. Treatment decisions should be made after discussing the appropriate options with the patient, taking into account their preference and convenience.

- The evidence base to direct first and second line treatments is not strong.
- All treatments have significant failure and relapse rates.
- Treatment may involve discomfort and local skin reactions. Written information on management of treatment side effects is recommended.
- Soft non-keratinised warts respond well to podophyllin, podophyllotoxin, and trichloroacetic acid.
- Keratinised lesions are better treated with physical ablative methods such as cryotherapy, excision, or electrocautery⁽²¹⁾

- Imiquimod may be suitable for both keratinised and non-keratinised warts.
- People with a small number of low volume warts, irrespective of type, are best treated with ablative therapy from the outset.
- Podophyllotoxin, for 4 week cycles, and imiquimod for up to 16 weeks are suitable for home treatment by patients. If chosen, the patient should be given a demonstration on lesion finding and treatment application.
- Local anaesthetic creams plus or minus injection with an injectable local anaesthetic (e.g. 2% lignocaine) could be used before ablative therapy to minimise discomfort. Adrenaline-containing anaesthetic should be avoided for lesions on the penis and around the clitoris.
- No treatment is an option at any site and may apply particularly to warts in the vagina and anal canal.
- Practitioners should consider developing a treatment algorithm or protocol. This has been shown to significantly improve clinical outcome.²²

Treatments available

Clearance and recurrence rates for individual treatments are shown in table 1⁽²³⁾.

Table 1 Overview of clearance and recurrence rates in the published literature with different treatments for external genital warts

Treatment	Clearance rates (%)		Recurrence rates (%)
	End of treatment	>3 months	
Cryotherapy	63-88	63-92	0-39
Electrocautery/electrotherapy	93-94	78-91	24
Laser therapy	27-89	39-86	<7-45
LEEP	<90	-	-
Podophyllotoxin* (Podofilox)	42-88	34-77	10-91
Imiquimod	50-62	50-62	13-19
Surgical/scissor excision	89-93	36	0-29
TCAA	50-81	70	36

(LEEP = loop electrical excision procedure; TCAA = trichloroacetic acid)

*Studies using more than one treatment strength have been grouped together. Studies are not comparable in design or method.

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When interpreting this table it is important to take into account that studies are not strictly comparable as methods and endpoints differ across the studies.

Chemical applications

Podophyllin

Podophyllin is a non-standardised cytotoxic compound. It has been associated with severe local reactions. Serious systemic adverse events have occurred when used outside guidelines⁽²⁴⁾. Podophyllin is licensed for prescription use only. Best practice described in the British National Formulary recommends supervised application in GU medicine clinics or general practice by trained nurses after screening for other STIs. Animal experiments indicate teratogenic and oncogenic properties⁽²⁵⁻²⁹⁾ but evidence of these in humans is lacking

- 15-25% solution can be carefully applied to lesions, in clinic, once or twice weekly. Wash off 4 hours later (Ib, A)

Caution:

- Podophyllin has caused serious systemic side effects if applied in excess. Increased systemic absorption is likely if used internally. Limit application to 10 cm² or 0.5 ml for external warts, and less than 2 cm² for vaginal warts (IV, C)⁽³⁰⁾.
- The potential oncogenic and teratogenic effects as noted indicate it should be avoided on the cervix and in the anal canal, and in pregnancy (IV, C).

In view of the adverse problems associated with podophyllin and its inferior efficacy to podophyllotoxin⁽³¹⁻³⁴⁾ (IIa, B) - greater than 20% clearance in each of the quoted studies in favour of podophyllotoxin – we would no longer recommend its use in the routine management of ano-genital warts. This is in keeping with European opinion.⁽³⁵⁾

Combination therapy

Applications of Podophyllin in conjunction with cryotherapy is used in the UK⁽³⁶⁾ although there are no studies to validate this approach.

Podophyllotoxin

Podophyllotoxin (Warticon and Condyline), a purified extract of podophyllin in the form of a 0.5% solution or 0.15% cream. is suitable for home treatment

(Ib, A). It is licensed for 4 and 5 week courses respectively and supervision by medical staff is recommended when the lesion area treated is greater than 4 cm². Podophyllotoxin has a license for the treatment of genital warts but not extragenital lesions such as anal warts.

- Treatment cycles consist of twice daily application for 3 days, followed by 4 days' rest for 4 – 5 cycles.
- The cream may be easier for many patients to apply, especially at the anus.
- Discontinue treatment if significant side effects (e.g. soreness, ulceration).
- Unprotected sexual contact should be avoided soon after application because of a possible irritant effect on the partner
- Cost: 0.5% solution 3 ml to £12.88, 0.15% cream 5 g, £15.46.

Caution: Avoid in pregnancy.

Trichloroacetic acid

Trichloroacetic acid (TCA) 80-90% solution is suitable for weekly application in a specialist clinic setting only. It acts as a caustic agent resulting in cellular necrosis (Ib, A).

- An intense burning sensation may be experienced for 5-10 minutes after application.
- Ulceration penetrating into the dermis may occur, and it is therefore not recommended for large volume warts.
- TCA can be used at most anatomical sites.
- Approximate cost: 10 ml, £3.00.

Caution

- TCA is extremely corrosive to the skin. Careful application and protection of the surrounding skin with petroleum jelly is recommended. A neutralising agent, for example sodium bicarbonate, should always be available in case of excess application or spills.

5-Fluorouracil

5-Fluorouracil is a DNA anti-metabolite, available in a 5% cream. Its use is limited by severe local side effects, which may result in long term problems- for example, neovascularisation and vulval burning. It may be teratogenic and therefore should not be used in pregnancy.

As satisfactory alternatives exist, this treatment is no longer recommended for the routine management of ano-genital warts. (IV, C)

Interferons

Various regimens have been described using interferons alfa, beta, and gamma as creams and as intra-lesional or systemic injection (Ib, A).

- Its use is limited by expense, systemic side effects, and a variable response rate.
- Cyclical low dose injection used as an adjunct to laser therapy has resulted in a lower relapse rate⁽³⁷⁾.
- Interferons are not recommended for routine management of ano-genital warts and should only be used on expert advice. (IV, C)

Imiquimod

Imiquimod is an immune response modifier.

- Available as a 5% cream, it induces a cytokine response when applied to skin infected with HPV⁽³⁸⁾.
- Suitable for use on all external AGW but is not recommended for use in pregnancy or internally (Ib, A).
- Use in uncircumcised men has been shown to be safe⁽³⁹⁾.
- Cream is applied to lesions three times weekly and washed off 6-10 hours later for up to 16 weeks.
- Response to treatment may be delayed for some weeks.
- Clinical trials of imiquimod versus placebo have shown response rates comparable with other chemical agents (Ib, A).^(40,41) An apparently low relapse rate has not been compared in clinical trials against other currently available therapies.
- Recent studies suggest fewer recurrences in patients using Imiquimod pre or post surgical excision of lesions.^(42,43)
- Unprotected sexual contact should be avoided soon after application because of a possible irritant effect on the partner.
- Latex condoms may be weakened if in contact with imiquimod.
- Cost: £51.32 for 4 week course.

Caution: Not approved for use in pregnancy or internally.

Physical ablation

Excision (Ib, A)

- Removal of warts under local anaesthetic injection is particularly useful for pedunculated warts, and small numbers of keratinised ones at anatomically accessible sites. The use of an anaesthetic cream (e.g EMLA®) prior to injection is recommended.
- Haemostasis can be established using electrosurgery, silver nitrate or application of a haemostatic solution.
- Treatment can be repeated as required. This is a good method of treatment for small numbers of warts and may be underused⁽⁴⁴⁾

Cryotherapy (Ib, A)

- Using a liquid nitrogen spray or a cryoprobe causes cytolysis at the dermal epidermal junction resulting in necrosis.
- Treatment should be applied until a "halo" of freezing has been established a few millimetres round the treated lesion.
- A freeze, thaw, freeze technique should be used and lesions held frozen for 10-30 seconds, depending upon size.
- There are health and safety issues to be considered when storing and handling liquid nitrogen. Information and guidance may be obtained from the following sites: British Oxygen (www.bocindustrial.co.uk <<http://www.bocindustrial.co.uk>>), COSHH essentials (www.coshh-essentials.org.uk <<http://www.coshh-essentials.org.uk>>) and the Health & Safety Executive (www.hse.gov.uk <<http://www.hse.gov.uk>>).

Electrosurgery (Ib, A)

Three types are commonly used:

- Electrocautery results in burning of the treatment site and surrounding tissue.
- Hyfrecator acts by electrofulguration resulting in superficial charring and little dermal damage, or for deeper tissue penetration electro desiccation. These can be followed by curettage.

- Monopolar surgery- different waveforms can be generated, allowing desiccation, cutting, or coagulation. This results in a cleaner cut and less damage to surrounding tissue⁽⁴⁵⁾.

Caution: leave skin bridges between treatment sites to aid healing and minimise scarring.

Laser treatment (IIa, B)

- The carbon dioxide laser is especially suitable for large volume warts and can be used at difficult anatomical sites, such as the urethral meatus, or anal canal.⁽⁴⁶⁾
- This is a considerably more expensive treatment modality than electrocautery.

Caution:

All electrocautery and laser techniques result in a plume of smoke which has been shown to contain HPV DNA, which may potentially cause infection of the respiratory tract in operating personnel. Therefore, masks should be worn and adequate extraction provided during these procedures (IIb, B)⁽⁴⁷⁾.

Sexual partners

- Current sexual partner(s) may benefit from assessment as they may have undetected genital warts, undetected other STI, or need an explanation and advice about disease process in partner (III, B).
- Tracing of previous sexual partner(s) is not recommended.

Follow up

- Review is recommended at end of course to monitor response and assess need for changes in therapy. Patients frequently overestimate their response to treatment.⁽⁴⁸⁾ Patients whose original lesions have responded well to treatment but in whom new lesions are developing, can continue with current regimen.
- Change is indicated if (a) patient is not tolerating current treatment, (b) under 50% response to current treatment by six weeks (8-12 weeks for imiquimod). (IV; C)
- Relapses should be treated as appropriate to the lesion types.

Special considerations

Anatomical sites

Podophyllin and 5-fluorouracil are no longer recommended for internal lesions.

Intravaginal

- Cryotherapy, electrosurgery and trichloroacetic acid are recommended treatments.
- If podophyllin is used it should be applied carefully to no more than a total area of 2 cm² weekly.

Cervix

- Cervical intraepithelial neoplasia (CIN) has been documented in patients with cervical warts and for this reason some practitioners have recommended colposcopic assessment and biopsy.⁽⁴⁹⁾ The natural history of CIN may be different in women with cervical warts but no study data are available to support this. In keeping with the NHS Cervical Screening Programme, we would not recommend colposcopy in women with genital warts, including those with cervical lesions, unless there was diagnostic uncertainty or clinical concern.
- The following are appropriate treatment modalities for cervical warts: cryotherapy, electrosurgery, trichloroacetic acid, laser ablation or excision.

Urethral meatus

- If base of lesions seen, treatment with cryotherapy, electrosurgery, laser ablation, podophyllotoxin or imiquimod. Lesions deeper in the urethra should be surgically ablated under direct vision, which may require referral to a urologist.

Intra-anal

- Treatment options include trichloroacetic acid, cryotherapy, electrosurgery, and laser ablation. There have been anecdotal reports of successful use of intra-anal Imiquimod.

Pregnancy

- Avoid podophyllin, podophyllotoxin, and 5-fluorouracil because of possible teratogenic effects.
- Imiquimod is not approved for use in pregnancy.
- Treatment aims to minimise the number of lesions present at delivery to reduce the neonatal exposure to virus.

- Potential problems for children are the development of laryngeal papillomatosis⁽⁵⁰⁾ and ano-genital warts⁽⁵¹⁾
- Very rarely a caesarean section is indicated because of obstruction of the vaginal outlet with warts or the presence of gross cervical warts. Caesarean section is not indicated to prevent laryngeal papillomatosis/anogenital warts in the neonate as both conditions are rare.

Cervical cytology

- The National Health Service Cervical Screening Programme recommends that no changes are required to screening intervals in women with ano-genital warts
- Guidelines for the management of abnormal smears have been defined⁽⁵²⁾.

Immunosuppressed

- People with impaired cell mediated immunity, for example organ transplant patients or those with HIV infection, are likely to have poor treatment responses, increased relapse rates, and an increased risk of developing ano-genital intraepithelial neoplasia.
- Careful follow up is required in all these patients.

Auditable outcome measures

The use of a treatment protocol has been shown to improve the management of genital warts⁽²²⁾ It is recommended that a continuing audit cycle is adopted to ensure effective use of a protocol and for the incorporation of any new treatments available.

Recommended outcomes are:

- Adherence to protocol, 90% of patients
- Percentage of patients with original wart clearance at 3 months; 90%

Author and centre

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Potential conflicts of interest

Dr R Maw has acted as an adviser to 3M Pharmaceuticals and Stiefel who have sponsored his attendance at scientific meetings. He has also conducted clinical trials for 3M and Perstorp. Dr Fox has received sponsorship to attend scientific meetings and has participated in research sponsored by 3M Pharmaceuticals. Dr Nathan has conducted clinical trials for 3M Pharmaceuticals and has received sponsorship for attendance at scientific meetings. Dr D. Rowen has conducted clinical trials for 3M and Steifel. Dr Sonnex has conducted clinical trials for Stiefel and acted as an adviser to 3M pharmaceuticals. Dr Lacey has conducted clinical trials for Stiefel and acted as an adviser to 3M pharmaceuticals. Dr Gilson has conducted clinical trials for Stiefel.

Evidence base

OVID/Medline was searched for the years 1966-2006 using keywords "human papillomavirus," "genital warts," "epidemiology," "clinical manifestations," "treatment," "management," "laryngeal papillomatosis."

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