



GUIDELINES

2019 IUSTI-Europe guideline for the management of anogenital warts

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Abstract

This guideline is an update of the 2011 European Guideline for the Management of Anogenital Warts. It is intended to support best practice in the care of patients with anogenital warts by including evidence-based recommendations on diagnosis, treatment, follow-up and advice to patients. It is intended for use by healthcare professionals in sexual health-care or dermato-venereology clinics in Europe but may be adapted for use in other settings where the management of anogenital warts is undertaken. As a European guideline, recommendations should be adapted according to national circumstances and healthcare systems. Despite the availability of vaccine to prevent HPV types 6 and 11, the cause of >95% anogenital warts, they remain an important and frequent health problem. The previous systematic review of randomized controlled trials for anogenital warts was updated. The changes in the present guideline include the following: Updated background information on the prevalence, natural history and transmission of human papillomavirus (HPV) infection and anogenital warts. Key recommendations for diagnosis and treatment have been graded according to the strength of the recommendation and the quality of supporting evidence. 5-fluorouracil, local interferon and photodynamic therapy have been evaluated and included as potential second-line treatment options. Evidence of the impact of HPV vaccination on the incidence of anogenital warts has been updated.

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Introduction and methodology

This guideline is an update of the 2011 European Guideline for the Management of Anogenital Warts. It provides guidance for best practice in the care of patients with anogenital warts including evidence-based recommendations on diagnosis, treatment, follow-up and advice to patients. It is intended for use by healthcare professionals in sexual health-care or dermato-venereology clinics in Europe but may be adapted for use in other settings where the management of anogenital warts is undertaken. As a European guideline, recommendations should be adapted according to

national circumstances and healthcare systems. Care providers are encouraged to use this guideline to develop local treatment algorithms which take account of their healthcare setting, availability of treatments and needs of their patient population.

The treatment recommendations in the 2011 guidelines were based on a systematic review of randomized controlled trials (RCTs) of anogenital wart treatments. We updated the review using the strategy detailed in Table 1 to identify new studies published since the previous guideline. This was performed using MEDLINE and EMBASE (2009-present) on 13 May 2019. Existing

Table 1 Search strategy

Combine with AND search	Population (Combine with OR search)	Keywords: genital wart* anogenital wart* anogenital-wart* anogenital wart* *anal wart* condyloma* venereal wart Plus appropriate mapped/ MeSH headings
	Intervention (Combine with OR search)	Keywords: podophyllotoxin podofilox podophyllin cryotherapy liquid nitrogen imiquimod aldara TCA trichloroacetic acid BCA bichloroacetic acid curettage excision surgical removal laser electrosurgery electrocautery hyfrecation ablati* diathermy 5-fluorouracil polyphenon photodynamic *tretin* (to capture acitretin, tretinoin, isotretinoin) Retinoids Plus appropriate mapped/ MeSH headings

systematic reviews of anogenital wart treatments were also considered. We evaluated the evidence that supports our recommendations using the grading system (Table 2) proposed by the British HIV Association Guidelines Group.¹ We also reviewed the anogenital wart treatment guidelines produced by national groups in the United Kingdom, Germany and United States.^{2–4}

The protocol for the production of this guideline is available on the IUSTI website. (<https://iusti.org/wp-content/uploads/2020/04/ProtocolForProduction2020.pdf>).

Aetiology and transmission

Anogenital warts are benign proliferative lesions found on the epithelium of any part of the genitalia, anus or perianal area and may also involve the inguinal or pubic regions. They are caused by human papillomavirus (HPV) genotypes 6 and 11 in >95% of cases.⁵ Multiple HPV types may be present in anogenital warts including 'high risk' oncogenic genotypes such as 16 and 18,^{5,6} due to coinfection, but there is no evidence that high risk HPV types

Table 2 Grading of recommendations and the quality of evidence

Grade	Recommendation
1	A strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach
2	A weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values
Quality of evidence	
A	High-quality evidence that comes from consistent results from well-performed randomized controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect
B	Moderate-quality evidence from randomized trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias
C	Low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion of most potential sources of bias
D	Evidence based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate

cause genital warts. Anogenital warts are a significant public health problem with global estimates of incidence of 160–289 cases per 100 000 person years.⁷ Although Europe-wide data are lacking, estimates of annual incidence in several European countries range from 0.13% to 0.16% of the general population.⁸ Transmission rates of HPV between sexual partners are high and transmission may occur in the absence of visible warts.⁹ Anogenital infection with HPV is common, with a global prevalence of any HPV genotype of 11.7% estimated from cervical cytology samples.¹⁰ In most cases, the infection is asymptomatic and visible genital lesions develop only in a minority of those infected. However, longitudinal studies have recorded warts developing in 14.6–64.2% of those infected with HPV 6 or 11.^{11–13} The incubation period between incident genital HPV infection and the appearance of warts is highly variable but has been found to be shorter in women (median 2.9 months) than men (median 11.0 months).^{11,12}

Clinical features

Symptoms

Most patients notice only the presence of warts, which are otherwise asymptomatic. However, symptoms can include itching, bleeding or dyspareunia.

Physical signs

Typical warts appear as superficial papular lesions of 1–5 mm diameter. They may be flat or pedunculated, solitary or multiple. Multiple warts may form larger plaques, particularly in the immunosuppressed or if left untreated. Warts usually match the skin tone but may be more heavily pigmented. They may occur on any area of anogenital skin but commonly affect sites traumatized during sexual intercourse, such as the preputial cavity in men and posterior introitus in women.¹⁴ Anal canal warts are more common in men who have sex with men (MSM) reporting condomless anal intercourse or other sexual practices involving anal penetration.¹⁵ Perianal warts, however, are common in both sexes and can occur in the absence of a history of anal intercourse.¹⁶

Complications

Psychosexual impact The negative impact of genital warts on sexual activity and health related quality of life outcomes is well recognized.^{17–19} The condition may cause anxiety, guilt, anger and loss of self-esteem, and lead to concerns regarding future fertility and cancer risk.^{20,21}

Precancer and cancer Anogenital warts are by definition benign lesions which pose no risk of neoplastic change. However, both premalignant (vulval, anal and penile intra-epithelial neoplasia, i.e. VIN, AIN, and PIN) or malignant lesions can coexist or develop within wart lesions^{22,23} or, rarely, be misdiagnosed as warts. Clinical suspicion of neoplastic change should be aroused by bleeding or an atypical appearance including ulceration or palpable dermal infiltration. In such cases, urgent biopsy or specialist referral is warranted. Bowenoid papulosis is a condition characterized by reddish-brown lesions associated with oncogenic HPV types and is part of the clinical spectrum of anogenital intra-epithelial neoplasia.²⁴ A rare variant of HPV 6/11 disease is the giant condyloma or Buschke–Lowenstein tumour. This is a form of verrucous carcinoma which causes local infiltration into underlying dermal structures. The mainstay of management is surgical resection with or without adjuvant chemoradiotherapy, topical retinoids or imiquimod.²⁵ Specialist surgical and oncological involvement is required in these cases.

Diagnosis

- A good light source is recommended for examination (1D).
- Magnification with a lens or colposcope may be useful for small lesions (2D).
- Examination should include inspection of the urethral meatus (1D).
- In female patients presenting with anogenital warts, vaginal or cervical warts are present in an estimated 15% and 6% of individuals respectively.¹⁴ Speculum examination should be offered at initial assessment if cervical or vaginal lesions are suspected, such as when lesions are found at the introitus or

when the patient reports being aware of possible internal lesions (1D).

- Perianal inspection should be offered for both sexes at initial assessment or if there are symptoms (e.g. lesions or anal irritation are reported) (1D); digital rectal examination and proctoscopy should be offered if anal canal warts are suspected (e.g. external lesions extending into the anal canal; anal bleeding or discharge) (1D).
- Biopsy is not necessary for typical anogenital warts but is recommended if there is diagnostic uncertainty or suspicion of precancer or cancer (1D).
- The differential diagnosis of genital warts includes molluscum contagiosum and seborrhoeic keratoses as well as normal variants such as penile papules and Fordyce spots.
- Human papillomavirus detection or typing does not influence management and is not recommended
- Some practitioners use the acetic acid test to diagnose sub-clinical HPV lesions; its place in diagnosis and management is uncertain.²⁶

Management

Information, explanation and advice for the patient

Patients should be given a detailed explanation of their condition, including advice about onward transmission. (1D) This should be reinforced by offering them clear and accurate written information. (2D) A patient information leaflet has been produced by IUSTI. (<https://iusti.org/wp-content/uploads/2019/11/GenitalWarts2019.pdf>).

Treatments

Of the options available currently, only surgical treatment has a primary clearance rate approaching 100%. Recurrences occur after all therapies. Recurrence rates, including new lesions at previously treated or new sites, are often 20–30%, and increase with longer duration of follow-up. All topical treatments are associated with local skin reactions including itching, burning, erosions and pain.

Recommended treatments suitable for self-application Podophyllotoxin 0.5% solution (1A) and 0.15% cream (2A). Podophyllotoxin is self-applied to lesions twice daily for 3 days, followed by four rest days, for up to 4 or 5 weeks (according to the product licence). Common reactions include transient tenderness, erythema and erosions.^{27,28} Podophyllotoxin is contraindicated during pregnancy, and women of child-bearing age must be advised to use an effective method of contraception or abstain from vaginal intercourse during therapy. The use of podophyllotoxin to treat perianal warts is outside the product licence for either preparation, but is well-established in clinical practice. Clinical experience suggests that for ease of application the cream formulation is preferable for

vulval and perianal warts, therefore we suggest the use of podophyllotoxin cream for warts at these sites. A mirror and digital palpation can facilitate the application procedure.

Clearance rates of 36–83% for podophyllotoxin solution^{27–35} and 43–70% for podophyllotoxin cream^{28,33,34} have been reported. A recent systematic review and meta-analysis confirmed the effectiveness of podophyllotoxin 0.5% solution relative to placebo (RR: 19.86, 95% CI: 3.88–101.65).³⁶ They found the 0.5% solution to be superior to the 0.15% cream (RR: 1.26, 95% CI: 1.07–1.48) although the individual trials found them to be equivalent. However, neither the meta-analysis nor the included studies were stratified by the site of the warts. One study³⁵ compared podophyllotoxin solution against imiquimod 5% cream and found no difference in wart clearance, but the study was very small. A larger study comparing podophyllotoxin cream and imiquimod also found no difference when treatment with podophyllotoxin was extended for up to 16 weeks.³⁷ Recurrence rates of 6–100% have been reported with podophyllotoxin 8–21 weeks after clearance.^{27–30,32–34}

Imiquimod cream 5% (1A). Imiquimod cream is supplied as single use sachets. It is applied directly to the warts three times weekly prior to normal sleeping hours and washed off with soap and water between 6 and 10 h later. Treatment should continue until wart clearance, or for a maximum of 16 weeks. Local inflammatory reactions at the treatment site are common and may precede a treatment response. More severe reactions can be managed by interrupting treatment or by reducing the frequency of application. Severe reactions are uncommon but necessitate discontinuation of therapy.

In clinical studies, wart clearance has been reported in 35–75% of patients with treatment courses up to 16 weeks.^{35,38–44} The reported clearance rates are higher in women than in men, and women have a shorter median time to clearance than men. A recent Cochrane review of published RCTs found imiquimod to be superior to placebo in achieving complete clearance of warts (RR: 4.03, 95% CI: 2.03–7.99).⁴⁵ However, the reviewers judged all trials to be at high risk of bias and the review process was limited by heterogeneity of outcomes.

A systematic review assessing the optimum frequency of dosing has been published.⁴⁶ Daily dosing did not improve wart clearance when compared to three times weekly but did lead to a greater likelihood of treatment interruption due to local adverse reactions in women and uncircumcized men.

Two RCTs have evaluated lower concentrations of imiquimod cream (2.5% and 3.75%) applied daily for up to 8 weeks. Clearance rates were low for men (14.3% and 18.6%) and women (28.3% and 36.6%) for the 2.5% and 3.75% strength respectively.^{47,48} No RCT has directly compared either lower strength preparation with imiquimod 5%. Imiquimod 3.75% is available in Europe for the treatment of actinic keratoses but it is not licensed for the treatment of warts.

Relatively low recurrence rates (6–26%) after successful clearance have been reported^{38–40,42,44}, but one randomized controlled trial found no difference in recurrence compared to podophyllotoxin.³⁷

Animal studies with imiquimod have not revealed any teratogenic effects in rats or rabbits. Three case series of imiquimod use in pregnant women have been published^{49–51} and no adverse pregnancy outcomes or fetal abnormalities have been reported. Nevertheless, more data is needed before imiquimod cream can be recommended during pregnancy.

Sinecatechins (1A). Sinecatechins are derived from green tea leaves of the *Camellia sinensis* species containing the active ingredient epigallocatechingallate (EGCG; Polyphenon E[®], Mitsui Norin Company Ltd, Tokyo, Japan). The mechanism of action is uncertain but various immunomodulatory and antiproliferative properties have been proposed.^{52,53} EGCG is formulated as a 10% ointment which is marketed in most European countries as Veregen[®] (Aresus Pharma, Strausberg, Germany) and in the UK as Catephen[®] (Kora Healthcare, Swords, Ireland). A 15% ointment preparation is only available in the US. The ointment is applied three times daily until complete clearance, or for up to 16 weeks. It cannot be used for internal warts or in pregnancy.

Three double-blind placebo-controlled RCTs have evaluated the 15% ointment^{54–56} of which two also evaluated the 10% ointment. The study by Gross *et al.*⁵⁴ also assessed the efficacy of a 10% cream preparation for which wart clearance was not statistically greater than placebo. The trials found no difference in efficacy between the 10% and 15% ointment preparations. A meta-analysis of the three studies⁵⁷ concluded that both ointment preparations were efficacious relative to placebo. The reported clearance rates of 47–59% are similar to those observed with imiquimod. However, no head-to-head RCTs have been performed and comparison with other treatment trials is limited by heterogeneity of the study populations, as evidenced by the unusually high rates of spontaneous wart clearance in the sinecatechins trials.

Local reactions (most commonly itching and erythema) appear from week 2 of treatment and subside from week 4 onwards, are mostly of mild or moderate intensity and appear to be associated with a clinical response.⁵⁷ In those who clear warts, low recurrence rates (7–11%) were observed over 12 weeks of follow-up.^{54–56} There was an unusually high rate of spontaneous clearance in the placebo groups of all 3 studies.

There is a need for trials comparing sinecatechins with other treatments. Whether the dosing schedule is a barrier to patient adherence also needs to be assessed.

Recommended clinic-based treatments Cryotherapy (1A). Cryotherapy can be delivered by ‘open’ or ‘closed’ systems. Open application of liquid nitrogen is usually delivered by a spray gun

device to achieve freezing of the lesion and a margin of healthy skin for a duration of about 20 s. Closed cryoprobe systems utilize circulation of nitrous oxide or carbon dioxide, the probe gently pressed against the lesion moistened with saline or lubricating gel and freezing maintained until a 'halo' occurs a few millimetres around the lesion. Up to three freeze-thaw cycles may be applied to each lesion at each session, as tolerated by the patient. There is no standardized application technique and significant inter-operator differences exist. Cryotherapy is usually performed at weekly intervals until wart clearance, although no studies have systematically evaluated different treatment intervals.

Cryotherapy has the advantage of being simple to deliver if the equipment is available, inexpensive and safe in pregnancy. However, the likely need for repeated clinic visits, with the associated healthcare costs, is a disadvantage. Clinical studies report clearance rates of 44–87%^{58–66} and recurrence rates of 12–42% at 1–3 months and up to 59% at 12 months after clearance.⁶²

Several recent studies have compared wart clearance rates with cryotherapy against other treatments including trichloroacetic acid (TCA),⁶⁶ imiquimod,⁶² CO₂ laser⁶⁴ and potassium hydroxide.⁶⁵ Only CO₂ laser resulted in superior wart clearance compared to cryotherapy. A recent meta-analysis of studies comparing cryotherapy to other treatments found it to be slightly less efficacious than electrosurgery (pooled RR: 0.80; 95% CI: 0.65–0.99) but not different from TCA, podophyllin or imiquimod.⁶⁷ There was no comparison with podophyllotoxin included.

Trichloroacetic acid 80–90% solution (1A). Trichloroacetic acid is a corrosive agent. It is applied sparingly by a healthcare professional directly onto the wart surface with either a wooden or cotton tipped applicator. It is usually applied weekly. It is most suitable for small acuminate or papular warts but less easy to use on keratinized and large lesions. Excess application may cause scarring therefore protection of surrounding skin with petroleum jelly is advised. A neutralizing agent (e.g. 5% sodium bicarbonate) should be readily available in case of spills. When used optimally, a shallow ulcer forms that heals without scarring. Clearance rates of 56–94%^{58,61,66} and a recurrence rate of 36%⁵⁸ have been reported. TCA can be used safely during pregnancy.

Surgical treatment. A variety of surgical techniques are in use, including excision, electrosurgery, electrocautery and laser therapy. Surgery may be used as a primary therapy, and the majority of patients can be treated under local rather than general anaesthesia (e.g. 1–2% lidocaine for sub-cutaneous infiltration). The addition of adrenaline reduces bleeding but its use in the penis and in the clitoris region is controversial owing to the potential risk of necrosis.^{68–70} Its safety has not been established and clinics therefore may choose not to stock the combined preparations to prevent inadvertent use. When performed carefully, simple surgical approaches give highly satisfactory cosmetic results.

Electrosurgery, electrocautery and laser surgery should be performed with the use of surgical masks by the treatment team, and the use of an extractor fan due to the potential presence of infectious HPV particles in the smoke plume generated by these techniques. (1B).^{71,72}

Excision (1A)—Excision under local anaesthetic using scissors, scalpel or curettage is an option when small numbers of lesions are present and for exophytic or pedunculated warts. With the use of diathermy to control bleeding, suturing may not be required. Clearance rates of 89–100% have been reported for scissor excision, with recurrence rates of 19–29%.^{73–75} Large lesions, anal canal warts and lesions in children may require excision under general anaesthesia and should be referred to an appropriate surgical specialist.

Electrosurgery and electrocautery (1A)—Modern electrosurgical units utilize alternating current to produce different types of waveforms resulting in blends of cutting and coagulation. There are two main approaches:

- Electrocautery (also known as electrofulguration): the passage of a direct or alternating electric current through a resistant electrode tip which generates heat, the application of which leads to immediate tissue destruction. Any eschar can be removed with a curette.
- Electrosurgery (including hyfrecation): involves passing a high frequency alternating electrical current directly through an electrode tip. Direct contact of the tip with the lesion causes cutting and coagulation. Electrodesiccation is achieved by maintaining an air gap (1–3 mm) between the electrode tip and the lesion, leading to heating and carbonization of the tissue. As with electrocautery, any eschar can be removed with a curette.^{76,77}

Clearance rates of 94–100% and recurrence rates of 22% have been reported.^{59,78}

Laser surgery (1A)—Laser surgery uses a concentrated beam of infrared, or near infrared, light energy to heat and cauterize the affected area, and allows very high power densities to be delivered to small tissue volumes. The carbon dioxide (CO₂) laser and the neodymium–yttrium aluminium garnet (Nd-YAG) laser are in widespread use.⁷⁹ Clearance rates of close to 100% are usual although recurrence rates of 17–19% at 12 weeks and 66% at 12 months are comparable to other treatment modalities.^{64,80–82}

Therapies for which evidence is limited Therapies for which there is limited evidence are not generally recommended but may still be considered in cases unresponsive to standard therapies.

5-fluorouracil (2A). 5-fluorouracil (5FU) is an anti-metabolite which blocks DNA synthesis. It is available as a 5% cream which

is used to treat neoplastic and preneoplastic skin conditions including Bowen's disease and superficial basal cell carcinoma. A Cochrane review concluded that it is superior to placebo in achieving wart clearance but the authors state that the evidence provided by the current studies is weak.⁸³ It cannot be recommended for first-line use, but may be considered when other treatments have failed.

Intralesional/topical interferon (2A). There is no evidence for the use of systemic interferon for anogenital warts^{84,85}; however, studies of locally administered interferon, mostly using interferon alpha, have yielded some positive results.^{86–88} A meta-analysis of studies employing topical or injected intralesional interferon also found that they deliver superior clearance over placebo. We suggest that these treatments may be considered for refractory cases.⁸⁵

Combination therapies (2B). Treatments have often been used in combination.⁶¹ There is some theoretical rationale; for example, initial use of an ablative therapy may enhance local penetration of subsequent topical treatment, particularly for keratinized warts. Nonetheless, there is a lack of clinical trial evidence. In one placebo-controlled study, adjuvant podophyllotoxin cream following cryotherapy did not improve wart clearance at 4, 12 or 24 weeks post-treatment initiation.⁶³ Further evaluation of such treatment approaches is warranted, given the limited efficacy of most treatments and the frequency of recurrence.

Photodynamic therapy (2A). Photodynamic therapy (PDT) employs topical 5-aminolevulinic acid (ALA) as photosensitizer, followed by irradiation with red light to induce cell death or immunomodulation through generation of reactive oxygen species. Its uses include the treatment of actinic keratoses, basal cell carcinomas and Bowen's disease.⁸⁹ Studies of its use as adjuvant^{82,90} and stand-alone treatment^{80,81} in genital warts show some efficacy but there is not yet sufficient data to recommend this approach for first-line treatment.

Therapies not generally recommended Podophyllin. Podophyllin 20–25%, a non-standardized resin extract from the *Podophyllum* plant, is inexpensive to produce but is less effective than podophyllotoxin. Podophyllin preparations contain a variety of compounds some of which may be mutagenic⁹¹ and severe systemic toxicity after topical use has been described including death, intrauterine death, teratogenicity and neurological complications.⁹²

Treatment algorithms There is no single optimum treatment for anogenital warts. All modalities of treatment have advantages and limitations, and all are associated with a substantial risk of wart recurrence. Evaluation of the evidence is limited by the heterogeneity of study designs and reporting outcomes and a

lack of head-to-head comparisons between treatments. Patient-centred outcomes, in particular satisfaction with treatment, have been largely overlooked. Future studies should address these limitations.

Clinicians who treat anogenital warts should have access to a range of home and clinic-based therapies. Choice of therapy depends on the site, morphology and extent of warts and patient preference and requires discussion between the physician and the patient. Warts may regress spontaneously so that no treatment, or deferring treatment is a management option. Patients need to be advised, however, that lesions may get larger, or spread, and there may be an impact on the likelihood of transmission.

Availability and cost may also dictate choice of treatment, and cost effectiveness will vary between healthcare systems. An extensive systematic review and meta-analysis proposed a strategy of initial treatment with podophyllotoxin solution 0.5% followed by CO₂ laser therapy second line as the most cost effective from a UK perspective.⁷⁷ Care providers are encouraged to develop local treatment algorithms which address the needs of their patient population and are deliverable with the resources available to the service. (1B) Implementation of such algorithms has been shown to improve outcomes.⁹³

Treatment in special situations Vaginal, cervical, intra-meatal, intra-anal warts (2C). Vaginal warts can be treated with either cryotherapy, TCA or any surgical treatment modality. Cervical warts require gynaecological referral and, if treatment is required, cryotherapy, TCA or any surgical treatment modality is also acceptable. Intra-meatal warts can be treated surgically (including excision, electrosurgery or laser ablation). Podophyllotoxin, imiquimod or cryotherapy are acceptable alternatives if the base of the lesion is clearly visible. Anal canal warts can be treated with cryotherapy, TCA or any surgical treatment. Imiquimod use is also possible with suitable patient motivation, but is not licensed for use at this site. Surgical referral may be required.

Treatment in pregnancy (1D). In pregnancy, warts may enlarge and multiply. Topical treatments should be avoided but ablation using cryotherapy, TCA or any surgical treatment modality is acceptable. The presence of warts rarely impacts on the mode of delivery unless there is obstruction of the birth canal due to very large warts. Liaison with the obstetrician in management is recommended in all cases. Spontaneous regression of genital warts is frequently seen in the puerperium. Delaying treatment until after delivery is common practice.

Juvenile onset recurrent respiratory papillomatosis is a very rare complication of vertically transmitted HPV, occurring in approximately 4/100 000 live births.⁹⁴ There is no proof that treatment of the mother diminishes this risk, although reduction of viral burden would seem prudent through treatment in cases of very extensive warts.

Treatment in immunocompromized patients (2A). Both HIV infection and other causes of systemic immunosuppression are associated with an increased incidence of warts. Moreover, the response to treatment in HIV-positive subjects is impaired, and recurrences after treatment are more common^{95,96} although whether this applies to those on effective HIV therapy with a normal CD4 count is not known. A recent systematic review and meta-analysis of treatments in HIV-positive patients found evidence to support imiquimod for the partial clearance of external warts only, highlighting the urgent need for further data in this group.⁹⁷ Repeated or prolonged treatments may be necessary.

Partner notification

Current partners of patients with anogenital warts should be offered clinical assessment for the presence of warts along with education and advice about HPV infection and screening for other sexually transmitted infections. (2D)

Follow-up (2D)

Evidence is lacking regarding the optimal schedule for follow-up and guidelines differ in their recommendations.^{3,4} We suggest that local management protocols incorporate medical review of cases at regular intervals, for example, every 4 weeks, until warts have resolved, with switching of treatments if an inadequate response is observed. Patients with immunodeficiency or who are otherwise immunocompromised may remain at increased risk of recurrence of HPV-related disease, even after successful treatment and clearance of wart lesions. Such patients should be counselled on the importance of self-surveillance for new lesions and regular clinical review should be considered on a case-by-case basis.

Prevention, health promotion and vaccination

- Patients with first episode genital warts should be offered sexually transmitted infection screening as per local guidelines. (1D)
- Female patients should be informed about cervical cytology screening as per local or national guidelines. (1D)
- Condoms have been shown to at least partially protect against the acquisition of anogenital warts.^{98,99} Whether condoms protect against HPV transmission *per se* is less clear⁹⁹ but some data suggest that male condom use may protect female partners against HPV acquisition.^{9,100} The prevalence of HPV DNA has also been shown to be lower in men who consistently use condoms.¹⁰¹ Condom use has been shown to accelerate disease resolution when both partners have type-concordant HPV infection.^{100,102,103} Therefore, condom use is recommended when either partner has genital warts until resolution of lesions; (1A) but patients should be advised that they offer only partial protection against onward transmission. (2A)

- Cigarette smoking is associated with an increased risk of genital warts in a dose dependent manner even after adjustment for sexual behaviour.¹⁰⁴ It is also associated with persistence of anogenital HPV infection.¹⁰⁵ Although there is no evidence that smoking cessation improves outcomes of wart treatment, there is a clear individual and public health rationale for advising smoking cessation. (1C)
- Vaccination with Gardasil[®] (MSD Vaccins, Lyons, France) and Gardasil9[®] (MSD Vaccins) both provide durable protection against HPV genotypes 6 and 11, which cause the majority of anogenital warts. A recent trial suggested that there may be a benefit in using vaccine in conjunction with topical imiquimod or podophyllotoxin for the treatment, or prevention of recurrence, of genital warts but this has not been established.³⁷ There is no evidence of benefit in those with HPV infection, but no clinical disease. Vaccination prior to sexual debut will maximize the protective benefits. Countries differ in their HPV vaccination strategies. However, substantial reductions in genital wart incidence in young women and heterosexual men have been observed in Australia following the introduction of Gardasil[®] (MSD Vaccins) vaccine for schoolgirls.¹⁰⁶ Unexpectedly, a reduction in genital wart episodes was also seen in women and heterosexual men aged 15–19 in the UK following introduction of the bivalent vaccine Cervarix[®] (GlaxoSmithKline Biologicals S.A., Rixensart, Belgium).¹⁰⁷

Composition of editorial board

Please see https://iusti.org/wp-content/uploads/2019/12/Editorial_Board.pdf.

List of contributing organizations

Please see <https://iusti.org/regions/europe/guidelines-introduction/>.

References

- 1 British HIV Association (BHIVA) Working Group for NHS Evidence Accreditation of BHIVA guidelines. British HIV Association (BHIVA) Guideline Development Manual. URL <https://www.bhiva.org/file/jgCacHqmuxZFL/GuidelineDevelopmentManual.pdf> (last accessed: 4 February 2019).
- 2 British Association for Sexual Health and HIV. UK National Guidelines on the Management of Anogenital Warts 2015 URL <https://www.bashh.org/documents/UK%20national%20guideline%20on%20Warts%202015%20FINAL.pdf> (last accessed: 4 February 2019).
- 3 Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines. URL <https://www.cdc.gov/std/tg2015/default.htm> (last accessed: 4 February 2019).
- 4 Gross GE, Werner RN, Becker JC *et al.* S2k guideline: HPV-associated lesions of the external genital region and the anus - anogenital warts and precancerous lesions of the vulva, the penis, and the peri- and intra-anal skin (short version). *J Dtsch Dermatol Ges* 2018; **16**: 242–255.
- 5 Ball SL, Winder DM, Vaughan K *et al.* Analyses of human papillomavirus genotypes and viral loads in anogenital warts. *J Med Virol* 2011; **83**: 1345–1350.

- 6 Brown DR, Schroeder JM, Bryan JT, Stoler MH, Fife KH. Detection of multiple human papillomavirus types in Condylomata acuminata lesions from otherwise healthy and immunosuppressed patients. *J Clin Microbiol* 1999; **37**: 3316–3322.
- 7 Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. *BMC Infect Dis* 2013; **13**: 39.
- 8 Forman D, de Martel C, Lacey CJ *et al*. Global burden of human papillomavirus and related diseases. *Vaccine* 2012; **30**(Suppl 5): F12–F23.
- 9 Burchell AN, Coutlee F, Tellier PP, Hanley J, Franco EL. Genital transmission of human papillomavirus in recently formed heterosexual couples. *J Infect Dis* 2011; **204**: 1723–1729.
- 10 Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis* 2010; **202**: 1789–1799.
- 11 Winer RL, Kiviat NB, Hughes JP *et al*. Development and duration of human papillomavirus lesions, after initial infection. *J Infect Dis* 2005; **191**: 731–738.
- 12 Arima Y, Winer RL, Feng Q *et al*. Development of genital warts after incident detection of human papillomavirus infection in young men. *J Infect Dis* 2010; **202**: 1181–1184.
- 13 Anic GM, Lee JH, Stockwell H *et al*. Incidence and human papillomavirus (HPV) type distribution of genital warts in a multinational cohort of men: the HPV in men study. *J Infect Dis*. 2011; **204**: 1886–1892.
- 14 Oriel JD. Natural history of genital warts. *Br J Vener Dis* 1971; **47**: 1–13.
- 15 Jin F, Prestage GP, Kippax SC *et al*. Risk factors for genital and anal warts in a prospective cohort of HIV-negative homosexual men: the HIM study. *Sex Transm Dis*. 2007; **34**: 488–493.
- 16 Sonnex C, Scholefield JH, Kocjan G *et al*. Anal human papillomavirus infection in heterosexuals with genital warts: prevalence and relation with sexual behaviour. *BMJ* 1991; **303**: 1243.
- 17 Drolet M, Brisson M, Maunsell E *et al*. The impact of anogenital warts on health-related quality of life: a 6-month prospective study. *Sex Transm Dis* 2011; **38**: 949–956.
- 18 Senecal M, Brisson M, Maunsell E *et al*. Loss of quality of life associated with genital warts: baseline analyses from a prospective study. *Sex Transm Infect* 2011; **87**: 209–215.
- 19 Dominiak-Felden G, Cohet C, Atrux-Tallau S, Gilet H, Tristram A, Fiander A. Impact of human papillomavirus-related genital diseases on quality of life and psychosocial wellbeing: results of an observational, health-related quality of life study in the UK. *BMC Public Health* 2013; **13**: 1065.
- 20 Maw RD, Reitano M, Roy M. An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle. *Int J STD AIDS* 1998; **9**: 571–578.
- 21 Woodhall S, Ramsey T, Cai C *et al*. Estimation of the impact of genital warts on health-related quality of life. *Sex Transm Infect* 2008; **84**: 161–166.
- 22 Schlecht HP, Fugelso DK, Murphy RK *et al*. Frequency of occult high-grade squamous intraepithelial neoplasia and invasive cancer within anal condylomata in men who have sex with men. *Clin Infect Dis* 2010; **51**: 107–110.
- 23 Kreuter A, Siorokos C, Oellig F, Silling S, Pfister H, Wieland U. High-grade dysplasia in anogenital warts of HIV-positive men. *JAMA Dermatol* 2016; **152**: 1225–1230.
- 24 Ikenberg H, Gissmann LGross G, Grussendorf-Conen EI, zur Hausen H. Human papillomavirus type-16-related DNA in genital Bowen's disease and in Bowenoid papulosis. *Int J Cancer* 1983; **32**: 563–565.
- 25 Spinu D, Radulescu A, Bratu O, Checherita IA, Ranetti AE, Mischianu D. Giant condyloma acuminatum - Buschke-Lowenstein disease - a literature review. *Chirurgia (Bucuresti)* 2014; **109**: 445–450.
- 26 Kumar B, Gupta S. The acetowhite test in genital human papillomavirus infection in men: what does it add? *J Eur Acad Dermatol Venereol* 2001; **15**: 27–29.
- 27 Kirby P, Dunne A, King DH, Corey L. Double-blind randomized clinical trial of self-administered podofilox solution versus vehicle in the treatment of genital warts. *Am J Med* 1990; **88**: 465–469.
- 28 Claesson U, Lassus A, Happonen H, Hogstrom L, Siboulet A. Topical treatment of venereal warts: a comparative open study of podophyllotoxin cream versus solution. *Int J STD AIDS* 1996; **7**: 429–434.
- 29 Edwards A, Atma-Ram A, Thin RN. Podophyllotoxin 0.5% v podophyllin 20% to treat penile warts. *Genitourin Med* 1988; **64**: 263–265.
- 30 Beutner KR, Conant MA, Friedman-Kien AE *et al*. Patient-applied podofilox for treatment of genital warts. *Lancet* 1989; **1**: 831–834.
- 31 Mazurkiewicz WJS. Clinical efficacy of Condyline (0.5% podophyllotoxin) solution and cream versus podophyllin in the treatment of external condylomata acuminata. *J Dermatolog Treat* 1990; **1**: 123–125.
- 32 vonKrogh G, Szpak E, Andersson M, Bergelin I. Self-treatment using 0.25%–0.50% podophyllotoxin-ethanol solutions against penile condylomata acuminata: a placebo-controlled comparative study. *Genitourin Med* 1994; **70**: 105–109.
- 33 Strand A, Brinkeborn RM, Siboulet A. Topical treatment of genital warts in men, an open study of podophyllotoxin cream compared with solution. *Genitourin Med* 1995; **71**: 387–390.
- 34 Lacey CJ, Goodall RL, Tennvall GR *et al*. Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. *Sex Transm Infect* 2003; **79**: 270–275.
- 35 Komericki P, Akkilić-Materna M, Strimitzer T, Aberer W. Efficacy and safety of imiquimod versus podophyllotoxin in the treatment of anogenital warts. *Sex Transm Dis* 2011; **38**: 216–218.
- 36 Werner RN, Westfechtel L, Dressler C, Nast A. Self-administered interventions for anogenital warts in immunocompetent patients: a systematic review and meta-analysis. *Sex Transm Infect* 2017; **93**: 155–161.
- 37 Gilson R, Murray M, Meadows J *et al*. HIPvac: A randomised controlled trial of imiquimod or podophyllotoxin cream with HPV vaccine or placebo in the treatment and prevention of recurrence of anogenital warts. Poster IPV8-0882 presented at the 32nd International Papillomavirus Conference, Sydney, 2–6 October 2018. URL https://ipvc2018.org/PublishingImages/abstract-information/ipvc-2018-submitted-abstracts/IPVC18_-_All_abstracts_for_website.pdf (last accessed: 4 February 2019).
- 38 Beutner KR, Spruance SL, Hougham AJ, Fox TL, Owens ML, Douglas JM Jr. Treatment of genital warts with an immune-response modifier (imiquimod). *J Am Acad Dermatol* 1998; **38**(2 Pt 1): 230–239.
- 39 Beutner KR, Tying SK, Trofatter KF Jr *et al*. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. *Antimicrob Agents Chemother* 1998; **42**: 789–794.
- 40 Edwards L, Ferenczy A, Eron L *et al*. Self-administered topical 5% imiquimod cream for external anogenital warts. HPV Study Group. Human papillomavirus. *Arch Dermatol* 1998; **134**: 25–30.
- 41 Fife KH, Ferenczy A, Douglas JM Jr *et al*. Treatment of external genital warts in men using 5% imiquimod cream applied three times a week, once daily, twice daily, or three times a day. *Sex Transm Dis* 2001; **28**: 226–231.
- 42 Arican O, Guneri F, Bilgic K, Karaoglu A. Topical imiquimod 5% cream in external anogenital warts: a randomized, double-blind, placebo-controlled study. *J Dermatol*. 2004; **31**: 627–631.
- 43 Garland SM, Waddell R, Mindel A, Denham IM, McCloskey JC. An open-label phase II pilot study investigating the optimal duration of imiquimod 5% cream for the treatment of external genital warts in women. *Int J STD AIDS* 2006; **17**: 448–452.
- 44 Schofer H, Van Ophoven A, Henke U, Lenz T, Eul A. Randomized, comparative trial on the sustained efficacy of topical imiquimod 5% cream versus conventional ablative methods in external anogenital warts. *Eur J Dermatol* 2006; **16**: 642–648.

- 45 Grillo-Ardila CF, Angel-Muller E, Salazar-Diaz LC, Gaitan HG, Ruiz-Parra AI, Lethaby A. Imiquimod for anogenital warts in non-immunocompromised adults. *Cochrane Database Syst Rev* 2014; CD010389.
- 46 Gotovtseva EP, Kapadia AS, Smolensky MH, Lairson DR. Optimal frequency of imiquimod (aldara) 5% cream for the treatment of external genital warts in immunocompetent adults: a meta-analysis. *Sex Transm Dis* 2008; **35**: 346–351.
- 47 Baker DA, Ferris DG, Martens MG et al. Imiquimod 3.75% cream applied daily to treat anogenital warts: combined results from women in two randomized, placebo-controlled studies. *Infect Dis Obstet Gynecol* 2011; **2011**: 806105.
- 48 Rosen T, Nelson A, Ault K. Imiquimod cream 2.5% and 3.75% applied once daily to treat external genital warts in men. *Cutis* 2015; **96**: 277–282.
- 49 Einarson A, Costei A, Kalra S, Rouleau M, Koren G. The use of topical 5% imiquimod during pregnancy: a case series. *Reprod Toxicol* 2006; **21**: 1–2.
- 50 Audisio T, Roca FC, Piatti C. Topical imiquimod therapy for external anogenital warts in pregnant women. *Int J Gynaecol Obstet*. 2008; **100**: 275–276.
- 51 Ciavattini A, Tsioglou D, Vichi M, Di Giuseppe J, Cecchi S, Tranquilli AL. Topical Imiquimod 5% cream therapy for external anogenital warts in pregnant women: report of four cases and review of the literature. *J Matern Fetal Neonatal Med* 2012; **25**: 873–876.
- 52 Lin JK, Liang YC. Cancer chemoprevention by tea polyphenols. *Proc Natl Sci Counc Repub China B* 2000; **24**: 1–13.
- 53 Kuo CL, Chen TS, Liou SY, Hsieh CC. Immunomodulatory effects of EGCG fraction of green tea extract in innate and adaptive immunity via T regulatory cells in murine model. *Immunopharmacol Immunotoxicol* 2014; **36**: 364–370.
- 54 Gross G, Meyer KG, Pres H, Thielert C, Tawfik H, Mescheder A. 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**: 1404–1412.
- 55 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**: 1329–1338.
- 56 Tatti S, Swinehart JM, Thielert C, Tawfik H, Mescheder A, Beutner KR. Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol* 2008; **111**: 1371–1379.
- 57 Tzellos TG, Sardeli C, Lallas A, Papazisis G, Chourdakis M, Kouvelas D. 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**: 345–353.
- 58 Godley MJ, Bradbeer CS, Gellan M, Thin RN. Cryotherapy compared with trichloroacetic acid in treating genital warts. *Genitourin Med* 1987; **63**: 390–392.
- 59 Stone KM, Becker TM, Hadgu A, Kraus SJ. Treatment of external genital warts: a randomised clinical trial comparing podophyllin, cryotherapy, and electrodesiccation. *Genitourin Med* 1990; **66**: 16–19.
- 60 Handley JM, Maw RD, Horner T, Lawther H, McNeill T, Dinsmore WW. Non-specific immunity in patients with primary anogenital warts treated with interferon alpha plus cryotherapy or cryotherapy alone. *Acta Derm Venereol* 1992; **72**: 39–40.
- 61 Sherrard J, Riddell L. Comparison of the effectiveness of commonly used clinic-based treatments for external genital warts. *Int J STD AIDS* 2007; **18**: 365–368.
- 62 Stefanaki C, Katzouranis I, Lagogianni E et al. Comparison of cryotherapy to imiquimod 5% in the treatment of anogenital warts. *Int J STD AIDS* 2008; **19**: 441–444.
- 63 Gilson RJ, Ross J, Maw R, Rowen D, Sonnex C, Lacey CJ. A multicentre, randomised, double-blind, placebo controlled study of cryotherapy versus cryotherapy and podophyllotoxin cream as treatment for external anogenital warts. *Sex Transm Infect* 2009; **85**: 514–519.
- 64 Azizjalali M, Ghaffarpour GH, Mousavifard B. CO₂ laser therapy versus cryotherapy in treatment of genital warts; a randomized controlled trial (RCT). *Iran J Microbiol*. 2012; **4**: 187–190.
- 65 Camargo CL, Belda Junior W, Fagundes LJ, Romiti R. A prospective, open, comparative study of 5% potassium hydroxide solution versus cryotherapy in the treatment of genital warts in men. *An Bras Dermatol* 2014; **89**: 236–240.
- 66 Lotfabadi P, Maleki F, Gholami A, Yazdanpanah MJ. Liquid nitrogen cryotherapy versus 70% trichloroacetic acid in the treatment of anogenital warts: A randomized controlled trial. *Iran J Dermatol J* 2016; **18**: 151–155.
- 67 Bertolotti A, Dupin N, Bouscarat F, Milpied B, Derancourt C. Cryotherapy to treat anogenital warts in nonimmunocompromised adults: systematic review and meta-analysis. *J Am Acad Dermatol* 2017; **77**: 518–526.
- 68 Schnabl S, Herrmann N, Wilder D, Breuninger H, Häfner H-M. Clinical results for use of local anesthesia with epinephrine in penile nerve block. *J Dtsch Dermatol Ges* 2014; **12**: 332–340.
- 69 Kouba D, LoPiccolo MC, Alam M et al. Guidelines for the use of local anesthesia in office-based dermatologic surgery. *J Am Acad Dermatol* 2016; **74**: 1201–1219.
- 70 Wernham A, Shim TN. Survey of dermatologists and venereologists shows varying approach to penile biopsies. *J Clin Aesthet Dermatol* 2017; **10**: 26–27.
- 71 Ferenczy A, Bergeron C, Richart RM. Carbon dioxide laser energy disperses human papillomavirus deoxyribonucleic acid onto treatment fields. *Am J Obstet Gynecol* 1990; **163**(4 Pt 1): 1271–1274.
- 72 Park IU, Introcaso C, Dunne EF. Human papillomavirus and genital warts: a review of the evidence for the 2015 centers for disease control and prevention sexually transmitted diseases treatment guidelines. *Clin Infect Dis* 2015; **61**(Suppl 8): S849–S855.
- 73 Jensen SL. Comparison of podophyllin application with simple surgical excision in clearance and recurrence of perianal condylomata acuminata. *Lancet* 1985; **2**: 1146–1148.
- 74 Khawaja HT. Treatment of condyloma acuminatum. *Lancet* 1986; **1**: 208–209.
- 75 Khawaja HT. Podophyllin versus scissor excision in the treatment of perianal condylomata acuminata: a prospective study. *Br J Surg* 1989; **76**: 1067–1068.
- 76 Leung L. Hyfrecation for recalcitrant nongenital warts. *J Fam Med Prim Care* 2013; **2**: 141–144.
- 77 Thurgar E, Barton S, Karner C, Edwards SJ. Clinical effectiveness and cost-effectiveness of interventions for the treatment of anogenital warts: systematic review and economic evaluation. *Health Technol Assess* 2016; **20**: 1–486, v–vi.
- 78 Panici P, Scambia G, Baiocchi G, Perrone L, Pintus C, Mancuso S. Randomized clinical trial comparing systemic interferon with diathermocoagulation in primary multiple and widespread anogenital condyloma. *Obstet Gynecol* 1989; **74**(3 Pt 1): 393–397.
- 79 Gross GE, Barrasso R, eds. Human Papillomavirus Infection, A Clinical Atlas. Ullstein Mosby, Berlin, 1997.
- 80 Chen K, Chang BZ, Ju M, Zhang XH, Gu H. Comparative study of photodynamic therapy vs CO₂ laser vaporization in treatment of condylomata acuminata: a randomized clinical trial. *Br J Dermatol* 2007; **156**: 516–520.
- 81 Liang J, Lu XN, Tang H, Zhang Z, Fan J, Xu JH. Evaluation of photodynamic therapy using topical aminolevulinic acid hydrochloride in the treatment of condylomata acuminata: a comparative, randomized clinical trial. *Photodermatol Photoimmunol Photomed* 2009; **25**: 293–297.
- 82 Szeimies RM, Schleyer V, Moll I, Stocker M, Landthaler M, Karrer S. Adjuvant photodynamic therapy does not prevent recurrence of condylomata acuminata after carbon dioxide laser ablation - a phase III,

- prospective, randomized, bicentric, double-blind study. *Dermatol Surg* 2009; **35**: 757–764.
- 83 Batista CS, Atallah AN, Saconato H, da Silva EM. 5-FU for genital warts in non-immunocompromised individuals. *Cochrane Database Syst Rev* 2010; CD006562.
 - 84 Westfechtel L, Werner RN, Dressler C, Gaskins M, Nast A. Adjuvant treatment of anogenital warts with systemic interferon: a systematic review and meta-analysis. *Sex Transm Infect* 2018; **94**: 21–29.
 - 85 Yang J, Pu YG, Zeng ZM, Yu ZJ, Huang N, Deng QW. Interferon for the treatment of genital warts: a systematic review. *BMC Infect Dis* 2009; **9**: 156.
 - 86 Eron LJ, Judson F, Tucker S *et al*. Interferon therapy for condylomata acuminata. *N Engl J Med* 1986; **315**: 1059–1064.
 - 87 Friedman-Kien A. Management of condylomata acuminata with Alferon N injection, interferon alfa-n3 (human leukocyte derived). *Am J Obstet Gynecol* 1995; **172**(4 Pt 2): 1359–1368.
 - 88 Syed TA, Ahmadpour OA. Human leukocyte derived interferon-alpha in a hydrophilic gel for the treatment of intravaginal warts in women: a placebo-controlled, double-blind study. *Int J STD AIDS* 1998; **9**: 769–772.
 - 89 Chilakamarthi U, Giribabu L. Photodynamic therapy: past, present and future. *Chem Rec* 2017; **17**: 775–802.
 - 90 Mi X, Chai W, Zheng H, Zuo YG, Li J. A randomized clinical comparative study of cryotherapy plus photodynamic therapy vs. cryotherapy in the treatment of multiple condylomata acuminata. *Photodermatol Photobiomod Photomed* 2011; **27**: 176–180.
 - 91 Lin MC, Cheng HW, Tsai YC, Liao PL, Kang JJ, Cheng YW. Podophyllin, but not the constituents quercetin or kaempferol, induced genotoxicity in vitro and in vivo through ROS production. *Drug Chem Toxicol* 2009; **32**: 68–76.
 - 92 Lacey CJ. Therapy for genital human papillomavirus-related disease. *J Clin Virol* 2005; **32**(Suppl 1): S82–S90.
 - 93 Reynolds M, Fraser PA, Lacey CJ. Audits of the treatment of genital warts: closing the feedback loop. *Int J STD AIDS* 1996; **7**: 347–352.
 - 94 Lacour DE, Trimble C. Human papillomavirus in infants: transmission, prevalence, and persistence. *J Pediatr Adolesc Gynecol* 2012; **25**: 93–97.
 - 95 Cusini M, Salmaso F, Zerboni R *et al*. 5% Imiquimod cream for external anogenital warts in HIV-infected patients under HAART therapy. *Int J STD AIDS* 2004; **15**: 17–20.
 - 96 Viazis N, Vlachogiannakos J, Vasiliadis K, Theodoropoulos I, Saveriadis A, Karamanolis DG. Earlier eradication of intra-anal warts with argon plasma coagulator combined with imiquimod cream compared with argon plasma coagulator alone: a prospective, randomized trial. *Dis Colon Rectum* 2007; **50**: 2173–2179.
 - 97 Werner RN, Westfechtel L, Dressler C, Nast A. Anogenital warts and other HPV-associated anogenital lesions in the HIV-positive patient: a systematic review and meta-analysis of the efficacy and safety of interventions assessed in controlled clinical trials. *Sex Transm Infect* 2017; **93**: 543–550.
 - 98 Wen LM, Estcourt CS, Simpson JM, Mindel A. Risk factors for the acquisition of genital warts: are condoms protective? *Sex Transm Infect* 1999; **75**: 312–316.
 - 99 Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis* 2002; **29**: 725–735.
 - 100 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**: 811–816.
 - 101 Pierce Campbell CM, Lin HY, Fulp W *et al*. Consistent condom use reduces the genital human papillomavirus burden among high-risk men: the HPV infection in men study. *J Infect Dis*. 2013; **208**: 373–384.
 - 102 Bleeker MC, Berkhof J, Hogewoning CJ *et al*. HPV type concordance in sexual couples determines the effect of condoms on regression of flat penile lesions. *Br J Cancer* 2005; **92**: 1388–1392.
 - 103 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**: 804–810.
 - 104 Hansen BT, Hagerup-Jenssen M, Kjaer SK *et al*. Association between smoking and genital warts: longitudinal analysis. *Sex Transm Infect* 2010; **86**: 258–262.
 - 105 Nyitray AG, Carvalho da Silva RJ, Baggio ML *et al*. Six-month incidence, persistence, and factors associated with persistence of anal human papillomavirus in men: the HPV in men study. *J Infect Dis* 2011; **204**: 1711–1722.
 - 106 Chow EP, Read TR, Wigan R *et al*. Ongoing decline in genital warts among young heterosexuals 7 years after the Australian human papillomavirus (HPV) vaccination programme. *Sex Transm Infect* 2015; **91**: 214–219.
 - 107 Canvin M, Sinka K, Hughes G, Mesher D. Decline in genital warts diagnoses among young women and young men since the introduction of the bivalent HPV (16/18) vaccination programme in England: an ecological analysis. *Sex Transm Infect* 2017; **93**: 125–128.