British Association for Sexual Health and HIV national guideline for the management of Anogenital Warts in adults (2023)

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New in the 2023 Guideline

- All recommendations are rated according to the GRADE system, including those for the clinical evaluation, treatment and provision of advice for individuals presenting with anogenital warts
- Speculum vaginal examination only required if internal warts are suspected (due to vulvovaginal symptoms or warts which may extend into introitus)
- Recommendations provided for treatments not included in the 2015 guidelines: 5-fluorouracil cream, potassium hydroxide, photodynamic therapy and nitrizinc complex
- Podophyllotoxin solution (0.5%) is preferred over the 0.15% cream formulation where it can be easily applied owing to slightly superior efficacy
- Increased emphasis for patients with an inadequate response to treatment to switch to an alternative option, including a suggested upper limit of 4 cryotherapy treatment sessions
- We encourage expanded access to treatments with high clearance rates (such as laser, electrosurgery and surgical excision) particularly for patients with difficult to treat warts
- Updated review of evidence for the use of HPV vaccines in individuals with anogenital warts to improve clearance and/or prevent recurrence

Introduction and Methodology

Objectives

This guideline offers recommendations on diagnosis, treatment and health promotion principles needed for the effective management of human papillomavirus (HPV)-related warts at anogenital sites including the external genitals, vagina, cervix, urethra, perianus and anal canal. The guideline is aimed primarily at patients aged 16 years or older presenting to healthcare professionals working in level 3 sexual health services in the United Kingdom. However, the principles of the recommendations may be applied in other care settings, including in primary care, using locally adapted care pathways where appropriate. The management of HPV-related anogenital dysplasia or warts at other extragenital sites are outside the scope of this guideline.

Methods

This guideline was produced according to specifications set out in the "BASHH 2020 Framework for guideline development and assessment" accessed at https://www.bashhguidelines.org/media/1247/2020-guidelines-framework.pdf

The writing group formulated PICO (Patient/population, Intervention, Comparison, Outcome) questions as detailed in Appendix 1 which formed the basis of the literature search. A literature search for evidence published since drafting of the 2015 guidelines was performed using the search strategy detailed in Appendix 2 via the following databases: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). We prioritised evidence from randomised controlled trials (RCTs) and systematic reviews; non-

controlled studies, observational studies and case series were considered where evidence from RCTs was limited or absent. Guidelines from the International Union Against STIs (IUSTI-Europe), US Centres for Disease Control and Prevention (CDC) and national guidelines from Germany, Australia, New Zealand and Canada were also reviewed. The GRADE system was used to evaluate evidence and to formulate and rate the strength of recommendations.

Piloting and feedback

The first draft was produced by the writing group and then circulated to BASHH CEG for evaluation using the AGREE appraisal tool. The draft was also circulated to current members of the BASHH HPV SIG for expert review. The second draft of the guideline will be posted on the BASHH website for wider consultation for 2 months and simultaneously reviewed by the BASHH Public Panel. The draft guideline was also piloted in a sample of sexual health clinics.

Aetiology

Anogenital warts (AGW) are caused by the human papillomavirus (HPV) of which over 100 genotypes have been identified but around 90% of warts at the anogenital site are caused by HPV types 6 or 11. The mode of transmission is usually by sexual contact - transmission between sexual partners is common and also occurs in the absence of visible warts. (1) Longitudinal studies suggest that warts develop in 15–64% of those infected with HPV 6 or 11.(2-4) The time interval between genital HPV infection and the appearance of warts is highly variable but appears to be shorter in women (median 3 months) than men (median 11 months).(2, 4)

HPV can be transmitted perinatally and genital lesions resulting from transfer of infection from hand warts (HPV type 2) may also occur.(5) There is no good evidence for transmission via fomites. AGW are benign lesions. Some genital warts may contain additional oncogenic HPV types, but oncogenic HPV most commonly causes anogenital dysplastic lesions and cancers rather than typical warts. HPV infection is very common, but most infections do not result in visible genital tract lesions, and resolve spontaneously within a year.(2-4, 6) The estimated annual incidence of genital warts in developed world populations is about 0.15% of the adult population per year(7) with a prevalence of HPV around 3% in adult men in the USA.(8) The prevalence of HPV 6/11 in the UK has fallen in vaccinated groups with an associated 35% decline in the number of genital warts diagnosed between 2010-2019.(9) However, genital warts remain common with around 50,000 new cases treated each year in sexual health clinics in England.(9)

Clinical features

AGW are benign epithelial lesions usually up to 5mm in diameter.(10) Lesions are most often multiple and non-pigmented however different pigment patterns may occur, especially on keratinised skin. Four morphological types are described: condylomata acuminata (flesh-coloured, soft exophytic papillomatous lesions); keratotic warts (thickened horny papules); flat warts (macular lesions) and papular warts.(10) Lesions may be seen anywhere throughout the anogenital skin and mucosa including the vulva, vagina, cervix, urethral meatus and anal canal.(11) Extragenital sites affected by genital HPV subtypes include the lips, oral mucosa, oropharynx, larynx, conjunctivae and nasal cavity. Apart from

their presence, most warts are asymptomatic although symptoms such as itching, bleeding or pain can occasionally occur.

Diagnosis

Visual inspection is usually sufficient to diagnose warts although magnification using a colposcope or dermatoscope may be helpful for small lesions.(12) Biopsy may be needed where there is diagnostic uncertainty. Differential diagnosis includes anatomical variants (pearly penile papules, papillomatosis vulvae, Fordyce spots), other sexually transmitted infections (molluscum contagiosum, condylomata lata), benign skin lesions (fibroma, seborrheoic warts, naevi), pre-malignant and malignant conditions (intraepithelial neoplasia, Bowen's disease, carcinoma and malignant melanoma). AGW are by definition benign lesions. However malignant or pre-malignant lesions, such as intra-epithelial neoplasia, may co-exist within wart lesions. Where there are atypical features such as bleeding, ulceration or clinical suspicion of malignancy, urgent biopsy is recommended.

Remote diagnosis through photographs of lesions using telemedicine has significant potential for improving access to clinical care, but further evidence on accuracy and acceptability is required before the routine use of remote diagnosis can be recommended.(13)

Recommendations

We recommend that individuals presenting with new or recurrent warts are offered careful examination of the entire external anogenital area and urethral meatus with good illumination (1D)

We suggest that speculum examination is offered to those with warts at the introitus where the upper limit cannot be visualised, or in those with external warts and other vulvo-vaginal symptoms such as irritation, bleeding or discharge (2D)

We suggest that proctoscopy and digital anorectal examination are offered to those with warts at the anal margin where the upper limit cannot be visualised, or in those with external warts and other anal canal symptoms such as irritation, bleeding or discharge (2D)

We recommend that atypical clinical features and/or clinical suspicion of malignancy should prompt urgent biopsy of lesions (1D)

We suggest that biopsy is considered where there is diagnostic uncertainty or non-response to treatment (2D)

General advice

Patients should receive a comprehensive explanation of their condition to include information on the natural history, transmission and treatment of warts. This should be reinforced with up-to-date written advice (see BASHH Patient Information Leaflet). It is important to provide reassurance that AGW are distinct from pre-malignant or malignant lesions and that screening intervals remain unchanged for those eligible for the NHS Cervical Screening Programme. Consistent condom use can reduce onward transmission of HPV and the spread of warts to sexual partners.(14-16) Smoking is associated with increased AGW prevalence and incidence and a reduced clearance of HPV infection; higher AGW recurrence rates have also been shown in current smokers.(17, 18) The psychological impact of an AGW diagnosis is well described and may result in significant anxiety, depression and psychosexual dysfunction.(19-21)

153

154 ***Recommendations***

155 **We recommend that patients are offered a comprehensive verbal and written explanation**

156 **of their condition and management options (1D)**

157 **We recommend consistent condom use to reduce the risk of onward transmission of**

158 **warts and HPV to sexual partners (1B)**

159 **We recommend provision of smoking cessation advice (1B)**

160 **We recommend provision of psychological support to those who experience significant**

161 **distress related to their AGW diagnosis (1C)**

162

163 **Benefits of treatment**

164 The aims of treatment include the clearance of visible warts, the restoration of the normal

165 appearance of the anogenital skin and/or mucosa and the prevention of wart recurrence.

166 There is no evidence that treatment of warts reduces the risk of onward transmission to

167 sexual partners. As warts may spontaneously regress, deferral of treatment is acceptable if

168 this is the patient's preferred option.(22) All treatments may result in localised skin

169 reactions and/or scarring and therefore it may be preferable to defer treatment for very

170 small lesions and where the diagnosis is unclear.

171

172 **Choice of treatment**

173 AGW treatments include self-applied (topical) agents and clinician-applied therapies (topical

174 or ablative). The choice of treatment depends on treatment availability, patient preference,

175 volume and location of lesions and the patient's prior experience of and response to

176 treatment. There is no single best treatment for warts and direct comparisons of clearance

and recurrence rates between trials are problematic due to differences in study populations and protocols.

Treatment algorithms

The development of a local treatment algorithm has been shown to improve patient outcomes and is recommended, based on local availability of treatment options.(23) A suggested algorithm is shown in Appendix 3 which can be adapted according to availability of treatment options, clinician experience and patient preference.

In choosing between self-applied agents, podophyllotoxin and imiquimod appear broadly equivalent in safety and efficacy.(24-27) However its lower cost, shorter treatment duration and faster mode of action may make podophyllotoxin preferred as a first choice. Sinecatechins have similar clearance rates in trials(28-30) but no randomised head-to-head comparisons with other treatments have been performed and the frequency of dosing (three times daily) may be a barrier to adherence. Current pricing information for recommended self-administered agents is summarised in Table 1.

For clinician-applied treatments, the highest clearance rates have been observed for laser, electrosurgery and surgical excision which have also been shown in network meta-analyses comparing multiple treatments to be the most successful approach in clearing warts. (31, 32) Fewer treatment sessions are typically required to achieve wart clearance than with cryotherapy or trichloroacetic acid (TCAA). Whilst surgical treatments are likely to be of higher cost and to require specialist equipment and clinical expertise to deliver, their provision may be cost-effective for individuals with recurrent or recalcitrant warts.(33)

Table 1. Current drug tariffs for self-applied treatments for AGW recommended for first-line use (source: British National Formulary on-line available at: https://bnf.nice.org.uk/)

Active ingredient	Formulation	Brand name	Manufacturer	Price
Podophyllotoxin	0.5% solution	Condyline®	Takeda UK Ltd	£14.49 (3.5ml)
Podophyllotoxin	0.5% solution	Warticon®	Phoenix Labs Ltd	£14.86 (3ml)
Podophyllotoxin	0.15% cream	Warticon®	Phoenix Labs Ltd	£17.83 (5g)
Imiquimod	5% cream	Aldara®	Viatris UK Healthcare Ltd	£48.60 (4-week course, 12x250mg sachets) £194.40 (16-week course, 48 x250mg sachets)
Camelia sinensis (sinecatechins)	10% ointment	Catephen®	Kora Healthcare	£39.00 (15g)

Recurrence

Recurrence of warts following successful clearance can occur after any treatment modality and there is limited evidence that any specific treatment is associated with a reduced recurrence rate following initial clearance of warts.(31) Individuals with lesions at more than one anatomical site may be more likely to experience recurrence.(34) The addition of topical treatment following ablative therapy may reduce the risk of subsequent recurrence; the best evidence is for 4-8 weeks of imiquimod following CO2 laser.(35) However, evidence

is lacking to recommend this strategy following other forms of ablation or using other topical agents.

Recommendations

We recommend that patients are given a full explanation of the strengths and weaknesses of the treatment options available to them and are fully involved in choosing their treatment (1D)

We recommend that a local treatment algorithm is in place to support treatment decisions (1C)

We recommend that individuals with recalcitrant or persistently recurrent warts are prioritised for ablative treatment with laser, electrosurgery or surgical excision (1A)

We suggest that treatment with CO2 laser can be followed with a 4-8 week course of imiquimod to reduce the risk of subsequent recurrence (2A)

Recommended treatments

The following treatments are recommended for the treatment of external AGW.

Self-applied treatments

Imiquimod (1A) (25, 26, 36-39)

Imiquimod is an immune response modifier which acts via induction of alpha-interferon and other cytokines. In the UK it is available as a 5% cream preparation (Aldara®) supplied in sachets, each containing sufficient cream to cover 20cm^2 wart area. The cream should be applied three times weekly in a thin layer directly to wart tissue prior to normal sleeping

hours and washed off after 6-10 hours. Local skin reactions, most commonly erythema, excoriation and erosion, occur 70-80% of treated individuals and correlate with clinical response. Treatment should be applied until disappearance of warts for a maximum of 16 weeks. It has the potential to exacerbate inflammatory skin conditions and should be used with caution in solid organ transplant recipients and in individuals with autoimmune conditions.

Recommendations

We suggest that where individuals have a <50% reduction in wart volume after 8 weeks' of imiquimod, a switch to an alternative treatment should be considered (2B)

Podophyllotoxin (1A) (27, 40-46)

Podophyllotoxin is an anti-mitotic agent which arrests mitosis in metaphase leading to epithelial cell death of virally infected cells. It is available as 0.5% solution or 0.15% cream which should be applied twice daily directly to lesions on three consecutive days, repeated weekly for a maximum of 5 or 4 weeks for the solution or cream respectively. Recent RCT evidence suggests it can be continued beyond this licensed duration to achieve maximal wart clearance.(27) Although it is not licensed for use on perianal lesions, RCT evidence suggests podophyllotoxin is safe and effective at this site.(27, 47, 48) The cream preparation is preferable for ease of application at perianal and other difficult to reach sites although has been shown to have slightly inferior efficacy to solution.(25, 32) Local skin reactions are common and it may be caustic to normal skin.

Recommendations

We suggest that podophyllotoxin solution should be preferred over the cream formulation at easy to reach sites owing to slightly superior efficacy (2A)

We recommend that podophyllotoxin 0.15% cream may be used for the treatment of external perianal warts on an off-license basis (1B)

We recommend that podophyllotoxin can be continued beyond its licensed duration where there is >50% wart clearance following 4-5 weeks of treatment (1A)

We suggest that petroleum jelly may be applied to healthy skin adjacent to lesions to limit damage from inadvertent contact with podophyllotoxin solution (2D)

Sinecatechins (1A) (28-30, 49)

Sinecatechins is the extract of *Camellia sinensis* (green tea) plant and contains the active ingredient epigallocatechingallate. Its mechanism of action is not fully known. It is available in the UK as a 10% ointment (Catephen®) which is applied directly to warts three times daily until clearance, for a maximum duration of 16 weeks. It is not necessary to wash the ointment off the affected area prior to the next application. Mild inflammatory reactions are common following application and correlate with clinical response.

Recommendations

We suggest that where individuals have a <50% reduction in wart volume after 8 weeks' of sinecatechins, switch to an alternative treatment should be considered (2B)

Clinician-applied treatments

Cryotherapy (1A) (50-60)

Cryotherapy destroys warts by thermal induced cytolysis and is usually available as a liquid nitrogen open spray or, less commonly, closed systems with a cryoprobe opposed directly against the lesion using nitrous oxide or CO2 cylinders. Portable canisters with alternative compressed gas formulations (Norfluorane/Dimethyl ether/propane) have become available more recently. These offer advantages over standard cryotherapy systems in their storage and maintenance, however no safety or efficacy data are yet available to support their use for AGW treatment.

Multiple treatment sessions may be required to achieve wart clearance. Systematic studies on the optimal frequency and application technique for cryotherapy are lacking although retrospective data suggest weekly treatment may reduce the total number of applications required versus longer intervals.(61) Local anaesthetic is not usually required although individuals may experience localised pain, blistering, pigment change or scarring following treatment.

Recommendations

We recommend that cryotherapy is given weekly with 1 or 2 freeze-thaw cycles performed per treatment session (1B)

A recommended freeze-thaw cycle should involve cautious application of the cryo-spray in brief bursts to achieve visible freezing of the lesion(s) and 1mm surrounding halo for up to 20 seconds followed by visible thawing (1B)

We suggest that where individuals have not achieved complete wart clearance after 4 cryotherapy sessions, switch to an alternative treatment should be considered (2C)

Laser (1A) (24, 31, 32, 55, 62, 63)

Laser therapy destroys warts by inducing vascular thrombosis in dermal papillary vessels leading to destruction of keratinocytes. Destruction of the blood vessels results in release of pro-inflammatory cytokines that enhances the cellular immune response which may aid in eradication of HPV. In addition, ablative laser therapy uses longer wavelength laser that is absorbed by water and vaporises keratinocytes.

Four modalities of laser therapy are used for treatment of warts:

1. Pulsed dye
2. Neodymium-doped yttrium aluminum garnet (Nd:YAG)
3. Carbon dioxide (CO2)
4. Erbium-doped yttrium aluminum garnet (Er:YAG)

Pulsed dye and Nd:YAG lasers are non-ablative lasers which may be less effective for pigmented lesions and individuals with darker skin. CO2 and Er:YAG are ablative lasers.

Although comparative studies with other wart treatments are limited, evidence from systematic reviews and network meta-analyses suggest higher clearance rates than standard topical treatments or cryotherapy albeit at higher cost. Adequate room ventilation

and personal protective equipment (PPE) are required due to the potential presence of HPV virions in the smoke plume generated by treatment administration.(64, 65)

Recommendations

We recommend that local anaesthetic is administered prior to laser treatment for AGW (1B)

We recommend that exhaust ventilation and PPE including N95 or FFP2/3 particulate respirator are employed during laser treatment of AGW (1A)

Electrosurgery (1A) (32, 50, 60, 62, 66, 67)

Electrosurgery involves the use of electricity to destroy AGW. There are two types:

1. Electrocautery (thermocautery): A direct current is passed through a wire to generate heat used to destroy tissues. The most common technique is the loop electrosurgical excision procedure (LEEP) where the wire is in the form of a loop used to curette and cauterize tissues. Disposable cautery pens are also available that can be used for treatment of limited (<10) warts
2. True electrosurgery: A high frequency alternating current is passed from an electrode through the patient's skin to generate heat. Two techniques are used for treatment of AGW:
    a. Electrofulguration: The electrode is held 1-2mm from the surface of the lesion causing an arcing spark resulting in tissue carbonisation and destruction of the AGW with the formation of a thick eschar.

b. Electrodessication: The electrode is in contact with the tissue causing heating and dehydration of the superficial epithelium resulting in coagulation of tissue with minimal scarring and pigment loss

Although comparative studies with other wart treatments are limited, higher clearance rates than cryotherapy have been reported and a single treatment application is usually sufficient.

Recommendation

We recommend that local anaesthetic is administered prior to any electrosurgery treatment for AGW (1B)

We recommend that exhaust ventilation and PPE including N95 or FFP2/3 particulate respirator are employed during electrosurgery treatment for AGW (1A)

Surgical excision (1B) (24, 68-70)

Excision can usually be performed under local anaesthetic using scissors, scalpel or curettage. It may be particularly useful for small numbers of warts and for pedunculated lesions.

Trichloro-acetic acid (1A) (24, 51, 57, 58, 71)

Trichloro-acetic Acid (TCAA) in 80-90% solution is directly corrosive to tissue. It should be applied sparingly to warts by a clinician using a cotton-tip applicator or plastic loop in a single, brief application per treatment session. It is generally administered weekly and multiple treatment sessions are usually required to achieve clearance.

Recommendations

We recommend that TCAA should not be placed on or immediately adjacent to the examining couch to avoid the risk of spillage over the patient (1D)

We recommend that a neutralising agent (eg. Sodium bicarbonate) should be readily available in case of spills during TCAA treatment (1D)

We recommend that a local anaesthetic gel be applied to the treated area after treatment to reduce discomfort (1D)

We suggest that where individuals have achieved <50% wart clearance after 4 applications of TCAA, switch to an alternative treatment should be considered (1C)

Other treatments

The following treatments may be considered when recommended treatments are unavailable, unsuitable or have failed.

5-Fluorouracil (2A) (24, 72-77)

Topical 5-fluorouracil is a cytostatic agent licensed for the treatment of malignant and premalignant skin lesions including actinic keratoses and Bowen's disease. It is not licensed for the treatment of AGW but has been shown to be effective in various preparations in clinical trials with similar clearance rates to approved topical agents. In the UK it is available as a 5% cream preparation which is applied thinly once or twice daily for 3-4 weeks. Treatment response is characterised by inflammation and erosion followed by re-epithelialisation. Animal studies have demonstrated teratogenicity and it should not be used in pregnancy or in individuals attempting to father a child; females of child-bearing potential

should use effective contraception during and for 7 months following completion of treatment.

Potassium hydroxide (2A) (56, 74, 78)

Potassium hydroxide 5% is a strong alkali which is caustic to normal skin and has been shown to be effective in treating AGW. In trials it was self-applied once or twice daily via a cotton tip applicator for up to 12 weeks. In the UK it is available as an over-the-counter treatment for molluscum contagiosum (MolluDab®) but is not licensed for the treatment of AGW.

Photodynamic therapy (2A) (63, 79-81)

Photodynamic therapy (PDT) involves application of a topical photosensitive agent (eg. 5-aminolaevulinic acid) directly to lesions followed by exposure to a beam of light. This activates the agent resulting in production of free radicals and/or reactive oxygen species which destroy cells. In the UK it is used for the treatment of skin lesions including basal cell carcinoma, actinic keratoses and Bowen's disease. Efficacy and tolerability appear high in clinical trials in which it has been compared favourably to CO2 laser.

Nitrizinc complex (2B) (82-84)

Nitrizinc complex is a clinician-applied topical solution containing nitric acid and zinc/copper salts which has a caustic action on warts and has shown similar efficacy to cryotherapy in one RCT among 120 individuals with previously untreated warts of <5mm diameter on the external genitals or perianal area. Several large case series also support its efficacy and tolerability. Marketed in the UK as Verrutop® (Espère Healthcare Ltd), drops of the solution

425 are applied directly to warts via a capillary tube for up to four treatment sessions at 2-week
426 intervals.
427
428 **Treatments not recommended**
429 Interferon applied as a topical gel or intralesional injection have shown benefits over
430 placebo in the clearance of warts.(85) However none are currently available in the UK and
431 they are unlikely to offer significant advantage over other topical immunostimulant
432 therapies. Inosine Pranobex (Imunovir®) is an oral immune stimulant treatment licensed as
433 adjuvant treatment to ablative or topical therapy for AGW taken 1g three times daily for 14-
434 28 days. Several small studies show a marginal benefit in wart clearance but there is
435 insufficient evidence to recommend it for routine use.(86, 87)
436
437 **Warts at internal anatomical sites**
438 Management of internal urethral, cervical, vaginal or anal warts may be challenging as they
439 are often less accessible for clinical evaluation and the application/delivery of local
440 treatments. Moreover, as individuals with internal warts are often excluded from clinical
441 trials, the evidence base for treatments is largely limited to observational studies or case
442 series. Internal warts may be of less cosmetic concern therefore deferral of treatment is an
443 option for asymptomatic lesions. Nonetheless as visualisation of such lesions may be
444 difficult, clinicians should have a low threshold for biopsy where there is any diagnostic
445 uncertainty.

Surgical treatments (laser, electrocautery or excision) are acceptable for internal warts at any site and should be offered first-line where available.(88-90) For urethral warts, cryotherapy may be considered where the base of the wart is clearly visible on meatal eversion.(91) It is therefore important to examine the urethral orifice with a good light source (and meatoscope/otoscope if needed) to determine the size and proximity of lesions to the meatal opening. There is increasing evidence for the effectiveness of PDT for urethral warts.(92, 93) Cryotherapy and TCAA may be useful for the treatment of vaginal, cervical or anal warts, although fume extraction is required to maintain visibility of lesions during cryotherapy. Imiquimod, used off-license, appears to be safe and effective when applied internally for anal warts.(94, 95)

We recommend the following treatments are suitable for all urethral warts: surgical excision, laser, electrosurgery (1A)

We suggest that cryotherapy may be used for distal urethral warts where the base of the wart is clearly visible on meatal eversion (2C)

We suggest that PDT may be considered for distal urethral warts where clinical provision is available (2A)

We recommend the following treatments for vaginal warts: surgical excision, laser, electrosurgery, cryotherapy or TCAA (1B)

We recommend the following treatments for cervical warts: surgical excision, laser, electrosurgery, cryotherapy or TCAA (1A)

We recommend colposcopy examination of all suspected HPV-related cervical lesions to differentiate between low-grade and high-grade lesions (1C)

We recommend the following treatments for anal warts: surgical excision, laser, electrosurgery, cryotherapy, TCAA or imiquimod (1B)

Pregnancy & breastfeeding

AGW may increase in size and number during pregnancy. As warts may spontaneously resolve in the puerperium, deferral of treatment should be considered where acceptable to the patient. Where treatment is indicated, ablative treatments are preferred with most published data available for cryotherapy and laser.(96, 97) TCAA can also used as it is not absorbed systemically although clinical studies to support its use are lacking.

At present, no self-applied topical agent is licensed for use during pregnancy or breastfeeding. Although recent safety data for imiquimod and podophyllotoxin are reassuring,(96, 98) there is insufficient evidence to recommend either for routine use given the availability of safe and effective alternatives.

We recommend that the following treatments may be used safely during pregnancy and breastfeeding: cryotherapy, laser, electrosurgery, excision and TCAA (1C)

HPV can be transmitted vertically during delivery and although there is currently no evidence that treatment of HPV-related lesions reduces the risk of transmission, treatment may be considered to reduce the viral burden to the neonate. Caesarean section is not usually indicated to prevent neonatal transmission but may rarely be needed where there is obstruction of the birth canal.(96, 99) Juvenile-onset recurrent respiratory papillomatosis

(JORRP) is a rare complication of neonatal HPV infection usually caused by types 6 or 11 and estimated to affect 4.3/100,000 births.(100) A history of maternal AGW is a strong risk factor and rates of JORRP incidence are estimated at 6/1000 births from individuals with current or prior AGW.(101) Delivery by caesarean section has not been shown to be protective and is not recommended.

We recommend that individuals with AGW during pregnancy should be reassured of the low absolute risk of significant HPV-related complications in the neonate (1C)

Immunocompromised patients

Immunocompromised individuals, including those living with advanced HIV (CD4 count<200) or organ transplant recipients, are at increased risk of AGW as well as other HPV-related conditions.(102, 103) Such individuals may present with more severe or extensive disease and clinicians should be alert to their higher risk of malignancy, particularly where lesions are atypical in appearance or fail to respond to treatment.(104) Nonetheless in view of the limited trial data for these populations, treatment recommendations do not differ from non-immunocompromised individuals.(105)

HPV vaccine

In the UK, HPV preventative vaccination was introduced in 2008 for girls aged 12-13 (with a catch-up programme for those up to 18 years of age) and extended to include boys in 2019. Two HPV vaccines which include coverage against genotypes 6 and 11 are currently licensed, the quadrivalent vaccine Gardasil® and nonavalent Gardasil®9 (Sanofi Pasteur

MSD). The quadrivalent vaccine (covering HPV 6/11/16/18) provides protection against the principal causes of both benign and malignant genital HPV disease and was used in the UK vaccine programme from 2012; from 2022 this was replaced by the nonavalent vaccine which offers extended coverage to HPV genotypes 31/33/45/52/58.

HPV vaccine is highly effective for the prevention of AGW when administered prior to coitarche, as demonstrated by the marked reduction in AGW incidence in age-groups offered vaccination via the UK school-based programme.(106) Trials have so far failed to demonstrate a significant therapeutic benefit of vaccine for those with existing warts either for clearance of warts or a reduction in subsequent recurrence.(27, 107, 108) The use of vaccine for the treatment of warts is therefore not recommended. However, in view of the clear benefits in reducing the risk of HPV-related anogenital intra-epithelial neoplasia and invasive cancer, we recommend that eligible individuals either with or without pre-existing AGW should be offered vaccination, in accordance with national guidance.(109)

Follow-up

Routine follow-up is not required for individuals whose warts have resolved. Follow-up should be arranged for individuals with warts still present at the end of treatment, or at 8 weeks following treatment initiation with imiquimod or sinecatechins.

Contact tracing and treatment

Routine evaluation or notification of sexual partners is not required for individuals with AGW.

Auditable outcomes

Adherence to a locally designed treatment procotol – target >90%

Proportion of individuals receiving cryotherapy completing 4 or fewer treatments - target >95%

Offer of speculum examination when vulvovaginal symptoms present or external warts at introitus that cannot be fully visualised – target 100%

Offer of proctoscopy and digital anorectal examination when anorectal symptoms present or external warts at anal margin that cannot be fully visualised – target 100%

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Editorial independence

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Declaration of conflicting interests

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1. 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(11):1723-9.
2. Arima Y, Winer RL, Feng Q, Hughes JP, Lee SK, Stern ME, et al. Development of genital warts after incident detection of human papillomavirus infection in young men. The Journal of infectious diseases. 2010;202(8):1181-4.
3. Anic GM, Lee JH, Stockwell H, Rollison DE, Wu Y, Papenfuss MR, et al. Incidence and human papillomavirus (HPV) type distribution of genital warts in a multinational cohort of men: the HPV in men study. The Journal of infectious diseases. 2011;204(12):1886-92.
4. Winer RL, Kiviat NB, Hughes JP, Adam DE, Lee SK, Kuypers JM, et al. Development and duration of human papillomavirus lesions, after initial infection. The Journal of infectious diseases. 2005;191(5):731-8.
5. Fairley CK, Gay NJ, Forbes A, Abramson M, Garland SM. Hand-genital transmission of genital warts? An analysis of prevalence data. Epidemiol Infect. 1995;115(1):169-76.
6. Massad LS, Xie X, Darragh T, Minkoff H, Levine AM, Watts DH, et al. Genital warts and vulvar intraepithelial neoplasia: natural history and effects of treatment and human immunodeficiency virus infection. Obstet Gynecol. 2011;118(4):831-9.
7. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30 Suppl 5:F12-23.
8. Daugherty M. Genital Wart and HPV Prevalence in Males in the United States from Penile Swabs: Results from NHANES. Sexually Transmitted Diseases. 2018;45(6):412-7.
9. Public Health England. Sexually Transmitted Infections: annual data tables 2021 [Available from: https://www.gov.uk/government/statistics/sexually-transmitted-infections-stis-annual-data-tables.
10. Gross G. Genitoanal human papillomavirus infection and associated neoplasias. Curr Probl Dermatol. 2014;45:98-122.
11. Oriel JD. Natural history of genital warts. Br J Vener Dis. 1971;47(1):1-13.
12. Errichetti E. Dermoscopy in Monitoring and Predicting Therapeutic Response in General Dermatology (Non-Tumoral Dermatoses): An Up-To-Date Overview. Dermatol Ther (Heidelb). 2020;10(6):1199-214.
13. Azfar RS, Lee RA, Castelo-Soccio L, Greenberg MS, Bilker WB, Gelfand JM, et al. Reliability and validity of mobile teledermatology in human immunodeficiency virus-positive patients in Botswana: a pilot study. JAMA Dermatol. 2014;150(6):601-7.
14. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sex Transm Dis. 2002;29(11):725-35.
15. Wen LM, Estcourt CS, Simpson JM, Mindel A. Risk factors for the acquisition of genital warts: are condoms protective? Sex Transm Infect. 1999;75(5):312-6.
16. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med. 2006;354(25):2645-54.
17. Kaderli R, Schnuriger B, Brugger LE. The impact of smoking on HPV infection and the development of anogenital warts. Int J Colorectal Dis. 2014;29(8):899-908.
18. Hansen BT, Hagerup-Jenssen M, Kjaer SK, Munk C, Tryggvadottir L, Sparen P, et al. Association between smoking and genital warts: longitudinal analysis. Sex Transm Infect. 2010;86(4):258-62.
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:

612 results of an observational, health-related quality of life study in the UK. BMC Public Health.
613 2013;13:1065.
614 20. Diaz ML. Counseling the patient with HPV disease. Obstet Gynecol Clin North Am.
615 2013;40(2):391-402.
616 21. Mortensen GL, Larsen HK. The quality of life of patients with genital warts: a
617 qualitative study. BMC public health. 2010;10:113.
618 22. Massad LS, Xie X, Darragh T, Minkoff H, Levine AM, Watts DH, et al. Genital warts
619 and vulvar intraepithelial neoplasia: natural history and effects of treatment and human
620 immunodeficiency virus infection. Obstet Gynecol. 2011;118(4):831-9.
621 23. Reynolds M, Fraser PA, Lacey CJ. Audits of the treatment of genital warts: closing the
622 feedback loop. Int J STD AIDS. 1996;7(5):347-52.
623 24. Bertolotti A, Milpied B, Fouere S, Cabie A, Dupin N, Derancourt C. Local management
624 of anogenital warts in immunocompetent adults: Systematic review and pooled analysis of
625 randomized-controlled trial data. J Am Acad Dermatol. 2019;81(5):1203-4.
626 25. Werner RN, Westfechtel L, Dressler C, Nast A. Self-administered interventions for
627 anogenital warts in immunocompetent patients: a systematic review and meta-analysis. Sex
628 Transm Infect. 2017;93(3):155-61.
629 26. Grillo-Ardila CF, Angel-Muller E, Salazar-Diaz LC, Gaitan HG, Ruiz-Parra AI, Lethaby A.
630 Imiquimod for anogenital warts in non-immunocompromised adults. Cochrane Database
631 Syst Rev. 2014(11):CD010389.
632 27. Gilson R, Nugent D, Bennett K, Dore CJ, Murray ML, Meadows J, et al. Imiquimod
633 versus podophyllotoxin, with and without human papillomavirus vaccine, for anogenital
634 warts: the HIPvac factorial RCT. Health technology assessment. 2020;24(47):1-86.
635 28. Gross G, Meyer KG, Pres H, Thielert C, Tawfik H, Mescheder A. A randomized,
636 double-blind, four-arm parallel-group, placebo-controlled Phase II/III study to investigate
637 the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external
638 genital warts. J Eur Acad Dermatol Venereol. 2007;21(10):1404-12.
639 29. Stockfleth E, Beti H, Orasan R, Grigorian F, Mescheder A, Tawfik H, et al. Topical
640 Polyphenon E in the treatment of external genital and perianal warts: a randomized
641 controlled trial. Br J Dermatol. 2008;158(6):1329-38.
642 30. Tatti S, Swinehart JM, Thielert C, Tawfik H, Mescheder A, Beutner KR. Sinecatechins,
643 a defined green tea extract, in the treatment of external anogenital warts: a randomized
644 controlled trial. Obstet Gynecol. 2008;111(6):1371-9.
645 31. Barton S, Wakefield V, O'Mahony C, Edwards S. Effectiveness of topical and ablative
646 therapies in treatment of anogenital warts: a systematic review and network meta-analysis.
647 BMJ Open. 2019;9(10):e027765.
648 32. Bertolotti A, Ferdynus C, Milpied B, Dupin N, Huiart L, Derancourt C. Local
649 Management of Anogenital Warts in Non-Immunocompromised Adults: A Network Meta-
650 Analysis of Randomized Controlled Trials. Dermatology And Therapy. 2020;10(2):249-62.
651 33. Thurgar E, Barton S, Karner C, Edwards SJ. Clinical effectiveness and cost-
652 effectiveness of interventions for the treatment of anogenital warts: systematic review and
653 economic evaluation. Health technology assessment. 2016;20(24):v-vi, 1-486.
654 34. Widschwendter A, Bottcher B, Riedl D, Coban S, Mutz-Dehbalaie I, Matteucci Gothe
655 R, et al. Recurrence of genitals warts in pre-HPV vaccine era after laser treatment. Arch
656 Gynecol Obstet. 2019;300(3):661-8.
657 35. Feng C, Li W, Wang X, Zhang H, Si L, Chen Z, et al. A systematic review evaluating the
658 efficacy and safety of a combination of ablative treatment and self administered treatment

versus ablative treatment alone for external anogenital warts. Int J Dermatol. 2020;59(10):1210-6.
36. Arican O, Guneri F, Bilgic K, Karaoglu A. Topical imiquimod 5% cream in external anogenital warts: a randomized, double-blind, placebo-controlled study. The Journal of dermatology. 2004;31(8):627-31.
37. Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. HPV Study Group. Human PapillomaVirus. Arch Dermatol. 1998;134(1):25-30.
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):230-9.
39. Beutner KR, Tyring SK, Trofatter Jr KF, Douglas Jr JM, Spruance S, Owens ML, et al. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. Antimicrob Agents Chemother. 1998;42(4):789-94.
40. Beutner KR, Conant MA, Friedman-Kien AE, Illeman M, Artman NN, Thisted RA, et al. Patient-applied podofilox for treatment of genital warts. Lancet. 1989;1(8642):831-4.
41. 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(5):465-9.
42. von Krogh 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(2):105-9.
43. 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(6):429-34.
44. 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(6):387-90.
45. Lacey CJ, Goodall RL, Tennvall GR, Maw R, Kinghorn GR, Fisk PG, 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(4):270-5.
46. Komericki P, Akkilic-Materna M, Strimitzer T, Aberer W. Efficacy and safety of imiquimod versus podophyllotoxin in the treatment of anogenital warts. Sex Transm Dis. 2011;38(3):216-8.
47. Hellberg D, Svarrer T, Nilsson S, Valentin J. Self-treatment of female external genital warts with 0.5% podophyllotoxin cream (Condyline) vs weekly applications of 20% podophyllin solution. International Journal of STD & AIDS.6(4):257-61.
48. Tyring S, Edwards L, Cherry LK, Ramsdell WM, Kotner S, Greenberg MD, et al. Safety and efficacy of 0.5% podofilox gel in the treatment of anogenital warts. Arch Dermatol. 1998;134(1):33-8.
49. 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(3):345-53.
50. 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(3):518-26.

51. Godley MJ, Bradbeer CS, Gellan M, Thin RN. Cryotherapy compared with trichloroacetic acid in treating genital warts. Genitourin Med. 1987;63(6):390-2.
52. Simmons PD, Langlet F, Thin RN. Cryotherapy versus electrocautery in the treatment of genital warts. Br J Vener Dis. 1981;57(4):273-4.
53. Sherrard J, Riddell L. Comparison of the effectiveness of commonly used clinic-based treatments for external genital warts. Int J STD AIDS. 2007;18(6):365-8.
54. Stefanaki C, Katzouranis I, Lagogianni E, Hadjivassiliou M, Nicolaidou E, Panagiotopoulos A, et al. Comparison of cryotherapy to imiquimod 5% in the treatment of anogenital warts. Int J STD AIDS. 2008;19(7):441-4.
55. Azizjalali M, Ghaffarpour G, Mousavifard B. CO(2) Laser therapy versus cryotherapy in treatment of genital warts; a Randomized Controlled Trial (RCT). Iran J Microbiol. 2012;4(4):187-90.
56. 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(2):236-40.
57. Abdullah AN, Walzman M, Wade A. Treatment of external genital warts comparing cryotherapy (liquid nitrogen) and trichloroacetic acid. Sex Transm Dis. 1993;20(6):344-5.
58. 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 Journal Translated Name Iranian Journal of Dermatology. 2016;18(4):151-5.
59. Golusin Z, Jovanovic M, Matic M, Ros T, Vujanovic L, Nikolic O. Clinical Efficacy of Combination Therapy with Podophyllotoxin and Liquid Nitrogen Cryotherapy in the Treatment of Genital Warts in Men. Acta Dermatovenerologica Croatica. 2019;27(4):250-9.
60. Stone KM, Becker TM, Hadgu A, Kraus SJ. Treatment of external genital warts: a randomised clinical trial comparing podophyllin, cryotherapy, and electrodesiccation. Genitourinary medicine. 1990;66(1):16-9.
61. Uyar B, Sacar H. Comparison of cryotherapy session intervals in the treatment of external genital warts. Dermatologica Sinica. 2014;32(3):154-6.
62. Ferenczy A, Behelak Y, Haber G, Wright TC, Jr., Richart RM. Treating vaginal and external anogenital condylomas with electrosurgery vs CO2 laser ablation. Journal of Gynecologic Surgery. 1995;11(1):41-50.
63. 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. British journal of dermatology. 2007;156(3):516-20.
64. Ferenczy A, Bergeron C, Richart RM. Human papillomavirus DNA in CO2 laser-generated plume of smoke and its consequences to the surgeon. Obstet Gynecol. 1990;75(1):114-8.
65. Fox-Lewis A, Allum C, Vokes D, Roberts S. Human papillomavirus and surgical smoke: a systematic review. Occup Environ Med. 2020;77(12):809-17.
66. Simmons PD, Langlet F, Thin RN. Cryotherapy versus electrocautery in the treatment of genital warts. British journal of venereal diseases. 1981;57(4):273-4.
67. Schoenfeld, A, Ziv, E, Levavi, H, et al. Laser versus loop electrosurgical excision in vulvar condyloma for eradication of subclinical reservoir demonstrated by assay for 2'5' oligosynthetase human papillomavirus. Gynecologic and obstetric investigation. 1995;40:46-51.

68. Jensen SL. Comparison of podophyllin application with simple surgical excision in clearance and recurrence of perianal condylomata acuminata. Lancet. 1985;2(8465):1146-8.
69. Khawaja HT. Podophyllin versus scissor excision in the treatment of perianal condylomata acuminata: a prospective study. Br J Surg. 1989;76(10):1067-8.
70. Khawaja HT. Treatment of condyloma acuminatum. Lancet. 1986;1(8474):208-9.
71. Sherrard J, Riddell L. Comparison of the effectiveness of commonly used clinic-based treatments for external genital warts. Int J STD AIDS. 2007;18(6):365-8.
72. Anggraini I, Hoemardani A, Nilasari H, Indriatmi W. Randomized controlled trial of 1% and 5% 5-fluorouracil compared to 90% trichloroacetic acid for anogenital wart treatment. Sex Transm Infect. 2019;95 (Supplement 1):A170-A1.
73. Batista CS, Atallah AN, Saconato H, da Silva EM. 5-FU for genital warts in non-immunocompromised individuals. Cochrane Database Syst Rev. 2010(4):CD006562.
74. Isik S, Koca R, Sarici G, Altinyazar HC. A comparison of a 5% potassium hydroxide solution with a 5-fluorouracil and salicylic acid combination in the treatment of patients with anogenital warts: a randomized, open-label clinical trial. Int J Dermatol. 2014;53(9):1145-50.
75. Relakis K, Cardamakis E, Korantzis A, Kotoulas I, Stathopoulos E, Metalinos K, et al. Treatment of flat or accuminata condylomata of the female genital tract with interferon alpha-2 alpha. Oncol Rep. 1996;3(5):951-5.
76. Wallin J. 5-Fluorouracil in the treatment of penile and urethral condylomata acuminata. Br J Vener Dis. 1977;53(4):240-3.
77. Syed TA, Qureshi ZA, Ahmad SA, Ali SM. Management of intravaginal warts in women with 5-fluorouracil (1%) in vaginal hydrophilic gel: a placebo-controlled double-blind study. Int J STD AIDS. 2000;11(6):371-4.
78. Asadi N, Hemmati E, Namazi G, Jahromi MP, Sarraf Z, Pazyar N, et al. A Comparative Study of Potassium Hydroxide versus CO2 Laser Vaporization in The Treatment of Female Genital Warts: A Controlled Clinical Trial. International Journal of Community Based Nursing & Midwifery. 2016;4(3):274-82.
79. 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. Photodermatology, photoimmunology & photomedicine. 2009;25(6):293-7.
80. Ying Z, Li X, Dang H. 5-aminolevulinic acid-based photodynamic therapy for the treatment of condylomata acuminata in Chinese patients: a meta-analysis. Photodermatology, Photoimmunology & Photomedicine. 2013;29(3):149-59.
81. Zhu X, Chen H, Cai L, Yu Z, Cai L. Decrease recurrence rate of condylomata acuminata by photodynamic therapy combined with CO2 laser in mainland China: a meta-analysis. Dermatology. 2012;225(4):364-70.
82. Pontini P, Mastorino L, Gaspari V, Granger C, Ramoni S, Delmonte S, et al. A Multicentre, Randomised Clinical Trial to Compare a Topical Nitrizinc((R)) Complex Solution Versus Cryotherapy for the Treatment of Anogenital Warts. Dermatol Ther (Heidelb). 2020;10(5):1063-73.
83. Cusini M, Micali G, Lacarrubba F, Puviani M, Barcella A, Milani M. Efficacy and tolerability of nitric-zinc complex in the treatment of external genital warts and "difficult-to-treat" warts: a "proof of concept", prospective, multicentre, open study. G Ital Dermatol Venereol. 2015;150(6):643-8.

84. Ciccarese G, Drago F, Granger C, Parodi A. Efficacy Assessment of a Topically Applied Nitric-Zinc Complex Solution for the Treatment of External Ano-genital Warts in 100 Patients. Dermatol Ther (Heidelb). 2019;9(2):327-35.
85. Yang J, Pu YG, Zeng ZM, Yu ZJ, Huang N, Deng QW. Interferon for the treatment of genital warts: a systematic review. BMC infectious diseases. 2009;9:156.
86. Davidson-Parker J, Dinsmore W, Khan MH, Hicks DA, Morris CA, Morris DF. Immunotherapy of genital warts with inosine pranobex and conventional treatment: double blind placebo controlled study. Genitourinary medicine. 1988;64(6):383-6.
87. Mohanty KC, Scott CS. Immunotherapy of genital warts with inosine pranobex (Imunovir): preliminary study. Genitourinary medicine. 1986;62(5):352-5.
88. Silvera RJ, Smith CK, Swedish KA, Goldstone SE. Anal condyloma treatment and recurrence in HIV-negative men who have sex with men. Diseases of the Colon & Rectum. 2014;57(6):752-61.
89. Henes M, Vogt B, Neis F, Rall K, Litzenburger T, Wallwiener D, et al. Application of a Thulium Laser for Treatment of Cervical Neoplasias and Condylomas: A Feasibility Study. Photomed Laser Surg. 2015;33(9):481-5.
90. Ferenczy A. Comparison of 5-fluorouracil and CO2 laser for treatment of vaginal condylomata. Obstet Gynecol. 1984;64(6):773-8.
91. Vives A, Vazquez A, Rajmil O, Cosentino M. Urethral condylomas in men: experience in 123 patients without previous treatment. Int J STD AIDS. 2016;27(1):39-43.
92. Xie J, Ao C, Li J, Jiang L, Liu H, Zeng K. 5-aminolevulinic acid photodynamic therapy for condyloma acuminatum of urethral meatus. Journal of Dermatological Treatment. 2019;30(7):714-7.
93. Shan X, Wang N, Li Z, Hou J, Zheng R, Tian H, et al. An open uncontrolled trial of topical 5-aminolevulinic acid photodynamic therapy for the treatment of urethral condylomata acuminata in male patients. Indian Journal of Dermatology, Venereology & Leprology. 2016;82(1):65-7.
94. Irisawa R, Tsuboi R, Saito M, Harada K. Treatment of intra-anal warts with imiquimod 5% cream: A single-center prospective open study. The Journal of dermatology. 2021;48(4):476-80.
95. Gkegkes ID, Iavazzo C, Stamatiadis AP. Intra-anal use of imiquimod: what is the clinical evidence? International Journal of STD & AIDS. 2019;30(10):1018-24.
96. Sugai S, Nishijima K, Enomoto T. Management of Condyloma Acuminata in Pregnancy: A Review. Sex Transm Dis. 2021;48(6):403-9.
97. Wilkerson EC, Van Acker MM, Bloom BS, Goldberg DJ. Utilization of Laser Therapy During Pregnancy: A Systematic Review of the Maternal and Fetal Effects Reported From 1960 to 2017. Dermatol Surg. 2019;45(6):818-28.
98. Andersson NW, Andersen JT. Association Between Fetal Safety Outcomes and Exposure to Local Podophyllotoxin During Pregnancy. JAMA Dermatol. 2020;156(3):303-11.
99. Medeiros LR, Ethur AB, Hilgert JB, Zanini RR, Berwanger O, Bozzetti MC, et al. Vertical transmission of the human papillomavirus: a systematic quantitative review. Cad Saude Publica. 2005;21(4):1006-15.
100. Lacour DE, Trimble C. Human papillomavirus in infants: transmission, prevalence, and persistence. J Pediatr Adolesc Gynecol. 2012;25(2):93-7.
101. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol. 2003;101(4):645-52.

102. Tyros G, Mastraftsi S, Gregoriou S, Nicolaidou E. Incidence of anogenital warts: epidemiological risk factors and real-life impact of human papillomavirus vaccination. Int J STD AIDS. 2021;32(1):4-13.
103. Gormley RH, Kovarik CL. Human papillomavirus-related genital disease in the immunocompromised host: Part I. J Am Acad Dermatol. 2012;66(6):867 e1-14; quiz 81-2.
104. 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. Clinical Infectious Diseases. 2015;61 Suppl 8:S849-55.
105. 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. Sexually Transmitted Infections. 2017:no pagination.
106. Checchi M, Mesher D, Mohammed H, Soldan K. Declines in anogenital warts diagnoses since the change in 2012 to use the quadrivalent HPV vaccine in England: data to end 2017. Sex Transm Infect. 2019;95(5):368-73.
107. Coskuner ER, Ozkan TA, Karakose A, Dillioglugil O, Cevik I. Impact of the quadrivalent HPV vaccine on disease recurrence in men exposed to HPV Infection: a randomized study. Journal of sexual medicine. 2014;11(11):2785-91.
108. Swedish KA, Goldstone SE. Prevention of anal condyloma with quadrivalent human papillomavirus vaccination of older men who have sex with men. PLoS ONE [Electronic Resource]. 2014;9(4):e93393.
109. Human papillomavirus (HPV): the green book, chapter 18a. Available at: https://www.gov.uk/government/publications/human-papillomavirus-hpv-the-green-book-chapter-18a [Accessed on 25th October 2022].

Appendix 1: List of PICO questions

1. What is the incidence of new and recurrent anogenital warts in adults in the UK?

2. What demographic, behavioural and co-morbidity factors are associated with anogenital warts?

3. What is the natural history of untreated HPV 6/11 infection?

4. How are HPV 6/11 and anogenital warts transmitted?

5. What is the risk of malignancy in patients presenting with anogenital warts?

6. In individuals with anogenital warts what type of examination will improve clinical outcomes such as wart clearance, identification of alternative or additional diagnoses, and improved patient satisfaction?

7. In individuals with anogenital warts what investigations will improve clinical outcomes such as wart clearance, identification of alternative or additional diagnoses, and improved patient satisfaction?

8. In individuals with anogenital warts what type of advice (content and mode of delivery) increases patient understanding and improves well-being?

9. In partners of individuals with anogenital warts what type of advice (content and mode of delivery) increases understanding and improves well-being?

10. What treatments are efficacious in the clearance and reduction of recurrence of anogenital warts?

11. What treatment options are preferred for anogenital warts according to their anatomical site or other clinical features?

12. In people with anogenital warts who are pregnant or lactating, what treatments are effective and safe?

908 **Appendix 2: Search strategy for literature review**

S1	MESH.EXACT.EXPLODE("Genital Diseases, Female") OR MESH.EXACT.EXPLODE("Genital Diseases, Male")
S2:	ti,ab(anogenital or genitoanal or genito-anal or genital* or anal or perianal or peri-anal or anus or urethra* or penis or penile or vulva* or vagina or vaginal or cervix or cervical or venereal)
S3	S1 OR S2
S4	MESH.EXACT("Warts")
S5	ti,ab(wart or warts or warty or verruca or verrucas or verrucae)
S6	S4 OR S5
S7	S3 AND S6
S8	ti,ab(condyloma*)
S9	ti,ab(lata or latum)
S10	S8 NOT S9
S11	MESH.EXACT("Condylomata Acuminata")
S12	S10 OR S11
S13	S7 OR S12
S14	MESH.EXACT("Disease Management") or MESH.EXACT("Treatment Outcome")
S15	ti,ab(treat* OR management OR therap* OR outcome*)
S16	S14 OR S15
S17	S13 AND S16
S18	(S17) and (la.exact("English"))
S19	(S17) and (pd(>20121231)) and (la.exact("English"))

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Appendix 3: Suggested treatment algorithm for external genital warts only in individuals who are not currently pregnant or breastfeeding