UK National Guidelines on the Management of Anogenital Warts 2015

Clinical Effectiveness Group
British Association for Sexual Health and HIV

Date of writing: April 2015
Date for review: April 2020

Guideline development group membership

- Lead author : Dr Richard Gilson
- Other members of the writing group: Dr Mayura Nathan, Dr Chris Sonnex, Dr Neil Lazaro, Tony Keirs

Lead author for BASHH CEG: Dr Neil Lazaro

What is new in the 2015 guidelines?

- Clearer advice on the choice of treatments
- Updated evidence on the efficacy of different treatment options
- Treatment algorithms for male and female patients

1. Introduction and methodology

- Objectives

The objectives of these guidelines are to provide recommendations on the diagnosis and treatment of benign ano-genital lesions caused by human papillomavirus (HPV) infection in men and women over 16 years of age. It does not deal with screening or treatment of pre-malignant or malignant ano-genital disease, or extra-genital HPV disease, which is beyond the scope of this guideline.

The guidelines are intended to apply to practice in Level 3 genitourinary medicine (GUM) /sexual health clinical services in the United Kingdom, but will also apply to other services where sexually transmitted infections may be managed, including primary care. Because of differences in the range of treatments available in different health care settings, it is important that providers develop local treatment algorithms based on these guidelines (in conjunction with their local Level 3 specialist service as necessary). These should ensure that there are appropriate clinical pathways for initial assessment and treatment, and for the management of those cases that do not respond promptly or relapse.

- Search strategy

OVID/Medline was searched for the years 1966-2013 using keywords "human papillomavirus," "genital warts," "epidemiology," "clinical manifestations," "treatment," "management".

- Methods

Article titles and abstracts were screened for relevance and the full text reviewed as appropriate. Priority was given to randomised controlled trial and systematic review evidence where these exist. Recommendations are graded on the basis of the best available current evidence.

- Piloting and feedback

These guidelines were compiled by a working group led by members of the BASHH *HPV Special Interest Group*. Amendments were included after they were reviewed by the HPV SIG members, a patient group at a GUM/HIV service, and the BASHH Patient & Public Engagement Panel.
The final guideline was then reviewed by the CEG using the AGREE instrument before posting it on the BASHH website for external peer review for a 2 month period. Comments received were collated by the CEG editor and sent to the guideline chair for review and action if necessary. The final guideline was approved by the CEG and a review date agreed before publication on the BASHH website.

- Review date

BASHH guidelines are generally updated every 5 years but the need for more frequent updates is considered annually by the CEG.

2. Aetiology

Anogenital warts are caused by the human papillomavirus (HPV) of which over 100 genotypes have been identified. The mode of transmission is most often by sexual contact but HPV may be transmitted perinatally and genital lesions resulting from transfer of infection from hand warts (HPV type 2) have been reported in children[1]. There is no good evidence of transmission from fomites. Anogenital warts are benign lesions and about 90% are caused by HPV types 6 or 11. Some lesions may contain oncogenic HPV types as well, but oncogenic HPV types most commonly cause anogenital dysplastic lesions and cancers. HPV infection is very common, but most infections do not result in visible genital tract lesions, and resolve spontaneously within a year. In a recent review, the estimated annual incidence of genital warts in developed world populations was about 0.15% of the adult population per year[2].

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). The bivalent vaccine used is intended to provide pre-exposure protection only against HPV 16/18 high risk types; there is no evidence of cross-protection against benign HPV-related disease. The quadrivalent vaccine (HPV 6/11/16/18) is intended to provide protection against the principal causes of both benign and malignant genital HPV disease and is being used in the vaccine programme in the UK (since 2012). Genital wart rates are expected to fall, at least in vaccinated cohorts, as has been reported elsewhere[3]. Genital warts remain however one of the most common conditions treated in GUM clinics with over 130,000 cases treated a year in the UK[4].

3 Clinical features

- Ano-genital warts are benign epithelial skin tumours. They may be single or multiple. Those on the moist, non-hair bearing skin tend to be soft and non-keratinised and those on the dry hairy skin, firm and keratinised. Lesions may be broad based or pedunculated and some are pigmented.
- HPV causes a multifocal infection of the ano-genital skin[5], lesions being most common at the site of trauma during sexual intercourse, but may occur at any genital or peri-genital site[6].
- Perianal lesions are common in both sexes and may not necessarily be associated with the practice of anal sex, due to the regional nature of infection with HPV. They are however seen more commonly in men who have sex with men (MSM)[6].
- Warts inside the anal canal are usually associated with penetrative anal sex[7].
- Asymptomatic lesions may be seen on the vagina, cervix, urethral meatus, and anal canal[6].
- Extra-genital lesions caused by genital HPV types may be seen in the oral cavity, larynx, conjunctivae, and nasal cavity; their management is beyond the scope of this guideline.

4. Presentation

Patients may present with symptoms related to their HPV-related anogenital disease, though many are asymptomatic. Symptoms include noticing the presence of new lumps/growths in the anogenital area. The incubation period is variable, but generally in the range 3 weeks to 8 months for the development of warts, but can be as long as 18 months, with some evidence that it is longer in men[8]. Some apparently new presentations will actually be recurrent disease. Other symptoms include local irritation, bleeding or discomfort. On rare occasions large warts present with secondary infection and maceration. More commonly warts present as soft cauliflower-like growths of varying size. Less commonly,

the warts are flat, plaque-like or pigmented. Rarely, warts may grow more rapidly and infiltrate local tissue or cause local erosion (Buschke-Lowenstein lesion).

5. Diagnosis

Although most warts are clinically recognisable, some lesions require examination under magnification (e.g. with a colposcope) to distinguish from other genital lumps (e.g. vestibular papillomatosis, molluscum contagiosum). Rarely, biopsy may be required to confirm the diagnosis in atypical lesions. It may be advisable to take a biopsy for histological verification in cases that do not respond to treatment. Examination of the genitalia and perianal skin is essential to recognise the full extent of the warts. In the presence of perianal warts, a proportion of patients will have warts in the anal canal. If patients have anal symptoms such as irritation or discharge, it is recommended to examine the anal canal.
Some patients present with intraepithelial neoplastic lesions in the anogenital region, either with or without coincidental benign warts. This includes intraepithelial neoplasia affecting the vulva (VIN), vagina (VaIN), perianal area (PAIN), anus (AIN) and penis (PIN). The diagnosis of intraepithelial neoplasia is made through histology. The presence of pigmentation, depigmentation, pruritus, underlying immune-deficiency, prior history of intraepithelial neoplasia on the same or distant anogenital sites, may raise suspicion of anogenital neoplasia.

6 Assessment of the patient with anogenital warts

- Examine the external ano-genital and surrounding skin under good illumination.
- Magnification (eg: with a colposcope) may be helpful in the case of small lesions or where the diagnosis is uncertain.
- Females should have a vaginal speculum examination as part of their initial assessment, but if no internal warts are found, internal examination is not required at follow-up.
- Routine proctoscopy is not required in patients presenting with genital warts. Proctoscopy is indicated in patients with warts at the anal margin where the upper limit cannot be visualised, or in those with other anal canal symptoms such as irritation, bleeding or discharge.
- Meatoscopy should be performed if there is difficulty in visualising the full extent of intra-meatal warts. Occasionally urethroscopy is indicated for more proximal warts.
- Extra-genital sites (e.g. oral cavity) should be examined if clinically indicated.
- Classify warts as to morphology
- Recording of lesions on genital maps at each visit is useful, providing a visual record of approximate number, distribution, to aid assessment of response to treatment.

7. Management

7.1 Limitations

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

While all possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration, it remains the responsibility of the prescriber to ensure the accuracy and appropriateness of the medication they prescribe.

7.2 General advice

- Patients should be given a detailed explanation of their condition. This should be reinforced by offering clear and accurate written information (see BASHH patient information leaflet).
- Consistent condom use has been shown to reduce the risk of acquisition of HPV infection and genital warts (in the order of 30-60% reduction)[9] [10] [11].They may reduce recurrence when both partners are infected[12] [13] [14], although the extent to which recurrence is due to re-infection is not known (IIIb; B)
- Latex condoms may be weakened if in contact with Imiquimod.
- For some patients the psychological impact of warts is the worst aspect of the disease[15]. Where psychological distress is apparent, referral for counselling may be appropriate.
- Smokers may respond less well to treatment than non-smokers [16] [17]
- Several treatment attempts are usually needed before warts subside.

7.3 Further investigations

Many patients will have other concurrent sexually transmitted infections (STIs), therefore, an appropriate screen for other STIs is recommended[18].

8. Treatment

8.1 General

- Treatment choice depends on the morphology, number, and distribution of warts and patient preference. Treatment decisions should be made after discussing the appropriate options with the patient. Treatments have been compared against no treatment or placebo, but comparative studies are very limited.
- The evidence base to direct first and second line treatments is not strong.
- All treatments have significant failure and relapse rates.
- Treatment may involve discomfort and local skin reactions. Provision of written information on management of treatment side effects is recommended.
- Soft non-keratinised warts respond well to podophyllotoxin, and trichloroacetic acid (TCA).

- Keratinised lesions may be better treated with physical ablative methods such as cryotherapy, excision, TCA or electrocautery[19]
- Imiquimod is suitable treatment for both keratinised and non-keratinised warts.
- People with a small number of low volume warts, irrespective of type, can be treated with ablative therapy or topical treatment with podophyllotoxin from the outset.
- Podophyllotoxin or Imiquimod are suitable for home treatment by patients. The patient should be given a demonstration on lesion finding and treatment application.
- Very large wart lesions, including Buschke-Lowenstein tumours, should be considered for surgical treatment.
- Injectable local anaesthetic (e.g. 2% lidocaine) should be used before any surgical excision or ablative procedure (other than cryotherapy). Topical anaesthetics (eg lidocaine cream, EMLA®) can be used prior to local anaesthetic injection. It can also be used prior to cryotherapy, particularly when treating larger lesions.
- Caution should be exercised using any modality of treatment because of the danger of oedema and necrosis of surrounding tissue. This is most pronounced with agents such as trichloroacetic acid, but can also be seen with other treatments including cryotherapy.
- No treatment may be an option, as about 30% of patients will experience spontaneous clearance of warts over a period of up to 6 months. However most patients seek treatment for the discomfort, anxiety, distress or the social unacceptability that warts cause.
- Practitioners should consider developing a treatment algorithm or protocol for their service. This has been shown to significantly improve clinical outcome[20]
- A treatment algorithm is included in the Appendix

8.2 Treatments available

Clearance and recurrence rates for individual treatments from published studies reviewed by Lacey et al are shown in Table 1[21]

There is a lack of comparative clinical trial data with which to make recommendations as to the preferred home-based and clinic-based treatments. The cost effectiveness of treatment options is discussed below.

Table 1: Summary of the results of randomized controlled trials of therapies for anogenital warts among HIV negative patients (modified from Lacey et al [21] with permission)

Treatment	Range of clearance rates based on an `intention to treat analysis`	Range of clearance rates based on a `per protocol analysis` (determined at time in weeks; range)	Range of recurrence rates (determined at time in weeks; range)
Podophyllotoxin solution 0.5%	45-83%	55-83% (3-6)	13-100% (8-21)
Podophyllotoxin cream 0.15%	43-70%	43-70% (4)	6-55% (8-12)
Imiquimod cream 5%	35-68%	55-81% (16)	6-26% (10-24)
Cryotherapy	44-75%	67-92% (6-10)	21-42% (4-12)
TCA	56-81%	81-84% (8-10)	36% (8)
Electrosurgery	94-100%	94-100% (1-6)	22% (12)
Scissors excision	89-100%	89-100% (6)	19-29% (40-48)

Note

1. Clearance rates and recurrence rates are not directly comparable as clearance was measured at different times from the start of treatment and high loss to follow up was often experienced in the trials.

2. The `intention to treat` analysis of clearance rates provides a conservative estimate of efficacy. The number enrolled into each group was taken as the denominator and the number known to have cleared as the numerator. For any missing data, participants were assumed not to be cleared. For the `per protocol analysis`, only those for whom follow-up data were available were included in the denominator and numerator; this may overestimate the efficacy.

8.3 Topical applications

8.3.1 Podophyllotoxin

Podophyllotoxin (Warticon® and Condyline®), a purified extract of podophyllin in the form of a 0.5% solution or 0.15% cream (Warticon® only), is suitable for self-application, and effective against genital warts (Ib, A). Warticon® and Condyline® are licensed for use for up to 4 and 5 weeks respectively and supervision by medical staff is recommended when the lesion area treated is greater than 4 cm^2. Podophyllotoxin is licensed for the treatment of warts affecting the penis and female external genitalia, but is commonly used for anogenital lesions at all sites.

- Treatment cycles consist of twice daily application for 3 days, followed by 4 days' rest, for 4 – 5 cycles.
- The cream and solution have similar efficacy however the cream may be easier for patients to apply, especially for less accessible lesions.
- Discontinue treatment if significant side effects (e.g. soreness, ulceration).
- Repeat cycles of treatment, although not licensed, may be considered if the warts are responding (see suggested algorithm)
- Unprotected sexual contact should be avoided soon after application because of a possible irritant effect on the partner

Caution: Avoid in pregnancy.

Note: Podophyllin is a non-standardised preparation which is not suitable for self-application and has worse efficacy and a higher incidence of local reactions than podophyllotoxin. It is no longer recommended.

8.3.2 Imiquimod

- Imiquimod is an immune response modifier. It acts as a toll-like receptor-7 (TLR7) agonist that results in stimulation of local tissue macrophages to release interferon-alpha and other cytokines as part of a local cell-mediated response.[22] It is available as a 5% cream: Aldara® (Meda).
- The cream is applied to lesions three times weekly and washed off 6-10 hours later, for up to 16 weeks.
- Response to treatment may be delayed for some weeks. Extending treatment to 20 weeks or beyond, in those who are showing a response, is common practice but there is no trial evidence concerning this.
- Clinical trials of Imiquimod versus placebo have shown response rates comparable with other topical agents (Ib, A).[23] [24] [25] A lower relapse rate has been suggested, but clinical trials comparing relapse after other topical therapies have not been conducted.
- Some studies suggest fewer recurrences in patients using Imiquimod in association with surgical excision of benign lesions[26] [27]and possible efficacy in the treatment of anogenital intra-epithelial

neoplasia, including AIN 2/3, but there is a lack of evidence from large randomised clinical trials[28 29].

- Unprotected sexual contact should be avoided soon after application because of a possible irritant effect on the partner.
- Latex condoms may be weakened if in contact with Imiquimod.
- The standard duration of treatment is 16 weeks. There is no data on the efficacy of its usage beyond 16 weeks.
- Immune deficiency may not be a contraindication for the use of Imiquimod topically for anogenital warts and it has been used in HIV positive subjects.
- Imiquimod frequently causes local skin / mucous membrane irritation when applied for anogenital warts. This may be due to narrow therapeutic margin. Temporary halting of treatment may be required to manage side effects.
- Non-responders by 12-16 weeks should be switched to an alternative treatment (see algorithm).
- Imiquimod has the potential to exacerbate inflammatory skin conditions; it should be used with caution in patients with autoimmune conditions although systemic absorption from topical treatment is likely to be negligible. No quantifiable levels of Imiquimod (>5 ng/ml) were detected in serum after single or multiple topical doses.

Caution: Not approved for use in pregnancy

8.3.3 Catephen® 10% ointment

Catephen® received a marketing authorisation in the UK in 2015. It is an extract of the leaf of the green tea plant *Camellia sinensis*, containing epigallocatechingallate (also known as Polyphenon E®, Veregen®, as marketed in other countries). The licensed indication is for the treatment of external genital warts in immunocompetent individuals. It is applied three times per day, for up to 16 weeks.

A combined analysis of two double blind, randomised placebo-controlled trials of topical treatment showed complete clearance of all baseline and new genital warts of 53.6%, compared to 35.4% in the vehicle-only control group, by intention-to-treat analysis. In those that cleared warts, recurrence rates over the 12 weeks from time of clearance, were similar in the control and active treatment groups (5.8 and 6.5% respectively)[30].

The mechanism of action is uncertain, but local reactions were common and more frequent in the active treatment arms in all studies, in keeping with other treatment modalities. There is no comparative data with other topical treatments but the trial results are consistent with a similar effect.

8.3.4 Trichloroacetic acid

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

- An intense burning sensation may be experienced for 5-10 minutes after application.

- Ulceration penetrating into the dermis may occur, and it is therefore not recommended for large volume warts.
- TCA can be used at most anatomical sites.

Caution:
- TCA is extremely corrosive. Careful application is essential.
- Protection of the surrounding skin with petroleum jelly should be considered and a topical neutralising agent, for example 5% sodium bicarbonate solution, available in case of excess application or spills.

8.3.5 5-Fluorouracil

5-Fluorouracil is a DNA anti-metabolite, available as a 5% cream. Its use is limited by local adverse effects, including chronic neovascularisation and vulval burning. It may be teratogenic and should not be used in pregnancy.

A Cochrane review concluded that 5-FU may still have a role in treatment, despite the inferior cure rates compared to combination therapies[31], however as satisfactory alternatives exist, this treatment is no longer recommended for the routine management of anogenital warts. (IV, C)

8.3.6 Interferons

Various regimens have been described using interferons alfa, beta, and gamma, as creams and as intra-lesional or systemic injections (Ib, A).
- Their use is limited by expense, systemic side effects, and a variable response rate.
- Cyclical low dose injection used as an adjunct to laser therapy has resulted in a lower relapse rate [32] however interferons are not recommended for routine management of anogenital warts and should only be used on expert advice. (IV, C)

8.4 Physical ablation

8.4.1 Excision (Ib, A)
- Removal of warts under local anaesthetic injection may be considered for pedunculated or large warts, and for small numbers of keratinised lesions at anatomically accessible sites.
- Haemostasis can be established using electrosurgery or the application of a haemostatic solution or paste (eg: ferric subsulphate – Monsel's solution).
- Treatment can be repeated as required.

This should be considered as a treatment option, particularly for the treatment of small numbers of warts, and may be underused[33]

8.4.2 Cryotherapy (Ib, A)
- Using a liquid nitrogen spray or a cryoprobe causes cytolysis at the dermal/epidermal junction resulting in necrosis.
- Treatment should be applied until a "halo" of freezing has been established a few millimetres around the treated lesion.
- Cryotherapy may be applied as a single freeze or a double freeze-thaw technique. There is no experimental evidence that the

technique used, or the duration of freezing (typically 15-30 seconds) affects the response rate, but it is reasonable to assume that a 'complete freeze' of the lesion should be achieved. This may take longer than 30 seconds and is likely to be limited by patient tolerability. Benign skin lesions, such as genital warts, may respond to a single treatment.

- Cryotherapy is usually repeated at weekly intervals; lack of response after 4 weeks should prompt consideration of an alternative treatment modality.

Caution: The storage and handling of liquid nitrogen should be undertaken according to health and safety guidance (see British Oxygen www.bocindustrial.co.uk), COSHH Essentials (www.coshhessentials.org.uk) and the Health & Safety Executive (www.hse.gov.uk)

8.4 3 Electrosurgery (Ib, A)

Three types are commonly used:

- Electrocautery results in burning of the treatment site and surrounding tissue.
- Hyfrecation acts by electrofulguration resulting in superficial charring and limited dermal damage; for deeper tissue penetration electro-dessication may be employed. These procedures can be followed by curettage.
- Monopolar surgery; different waveforms can be generated, allowing desiccation, cutting, or coagulation. This results in a cleaner cut and less damage to surrounding tissue[34].

Caution: leave skin bridges between treatment sites to aid healing and minimise scarring. Adequate ventilation should be provided for surgical procedures involving vaporisation, such as the use of an extraction hood.

8.4.4 Laser treatment (IIa, B)

- Laser treatment is especially suitable for large volume warts and can be used at difficult anatomical sites, such as the urethral meatus, or anal canal [35 36 37]
- Carbon dioxide laser is commonly used for external lesions, while internal lesions are treated with carbon dioxide or diode laser [35 37]
- This is a more expensive treatment modality compared to topical or other ablative methods[38].

Caution: All electrosurgical and laser techniques may generate a plume of smoke which has been shown to contain HPV DNA, which may potentially cause infection of the respiratory tract in the operating personnel. Therefore, masks should be worn and adequate extraction provided during these procedures (IIb, B)[39].

8.4.5 Combination therapy

Applications of podophyllotoxin or podophyllin in conjunction with cryotherapy have been used[40]. A randomised, double-blind, placebo controlled study of cryotherapy versus cryotherapy and podophyllotoxin cream as treatment for external anogenital warts has been published[41].

Clearance rates were higher in the combination arm (60% vs 45%) at 12 weeks, but at 24 weeks follow-up there was no difference in clearance rates.
Although sometimes used, there is no evidence on combining treatments in other ways such as applying cryotherapy once followed by treatment with a topical agent such as podophyllotoxin, or combining therapies such as TCA and cryotherapy.

8.5 HPV Vaccines

Three HPV vaccines are licensed in the UK. Gardasil® (Sanofi Pasteur MSD) is a quadrivalent vaccine providing protection against HPV 6, 11, 16 and 18, and has been used in the national HPV vaccine programme in the UK since 2012. Cervarix® (Glaxo SmithKline) is a bivalent vaccine providing protection against HPV 16 and 18. Gardasil9® (Sanofi Pasteur MSD) was licensed in Europe in 2015 and contains the same four antigens as Gardasil with five additional high-risk types (31, 33, 45, 52, and 58). All vaccines are licensed for the protection of individuals against genital infection and associated disease related to the vaccine-specific types. None of the vaccines are licensed for the treatment of existing HPV infection, or HPV-associated disease.

8.6 Other unlicensed and experimental treatments

8.6.1 Photodynamic therapy

Preliminary data is available on the use of photodynamic therapy with topical 5-aminolevulinic acid (ALA) for the treatment of anal canal warts[42]. There is insufficient evidence to make a recommendation on its use.

8.6.2 Tellurium immunomodulator AS101

This novel agent has been assessed for safety and efficacy in one study but there is insufficient data to make a recommendation[43].

8.6.3 Polyhexamethylene biguanide

One small randomised double-blind trial in 2005 found a clearance rate of 52% in the treated group compared to 4% in the placebo group[44]. Further data on this agent are not available.

9 Cost of treatment

Self-treatment costs are generally lower for the patient (less time spent attending clinic) and for health services (staff and other resource use). However the cost of treatment itself varies: podophyllotoxin cream or solution costs £12-£15 (for 4 weeks treatment) while the cost of imiquimod is up to £200 (for 16 weeks treatment). The materials cost of clinic based treatments such as cryotherapy are lower but will depend on usage, and the service delivery costs to the NHS are higher in cases where multiple clinic attendances are required. Cost-effectiveness analyses have been undertaken. They have produced conflicting results, are hampered by a lack of data on relative efficacy and are sensitive to changes in treatment and NHS costs[45 46 47]

10 Other management issues

10.1 Patient anxiety and distress

A diagnosis of anogenital warts can cause anxiety and distress. For some patients the psychological impact of warts is the worst aspect of the disease. Where psychological distress is apparent, referral for counselling may be appropriate.

10.2 Sexual partners

- Current sexual partner(s) may benefit from assessment as they may have undetected genital warts, other STIs, or need an explanation or advice about HPV infection r (III, B).
- Notification of previous sexual partner(s) is not recommended.

10.3 Follow up

- Review is recommended at the end of a treatment course to monitor response and assess the need for further therapy. Patients frequently overestimate their response to treatment[48]. Patients whose original lesions have responded well to treatment, but in whom new lesions are developing, can continue with the current regimen. Where there is no response, or only a partial response, by the end of the standard treatment duration, it is suggested that a second modality of treatment is applied (see Appendix for treatment algorithms).
- A change in therapy is indicated if either the patient is not tolerating the current treatment, or there is less than a 50% response to the current treatment by 4 to 5 weeks (8-12 weeks for Imiquimod). (IV; C)
- Relapses should be treated as appropriate to the lesion types.

10.4 Special situations

10.4.1 Intravaginal

- Cryotherapy, electrosurgery and trichloroacetic acid may be considered as treatment options. As for warts at other sites, particularly where they are asymptomatic, no treatment may also be considered as an option.
- Although not licensed for internal use, podophyllotoxin has been used, applied carefully to no more than a total area of $2cm^2$ weekly.

10.4.2 Cervix

The NHS Cervical Screening Programme guidelines do not recommend routine colposcopy in women with genital warts, including those with cervical lesions[49]. Colposcopy is indicated if there is diagnostic uncertainty. The following treatment modalities may be considered for cervical warts if required (no treatment is also an option): cryotherapy, electrosurgery, trichloroacetic acid, laser ablation or excision. If treated, repeat examination should be performed to confirm resolution.

10.4.3 Urethral meatus

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

10.4.4 Intra-anal

Treatment options include cryotherapy, topical Imiquimod (unlicensed indication), electrosurgery, laser ablation and trichloroacetic acid.

10.4.5 Management of warts in pregnancy and breastfeeding

Pregnancy

- Avoid podophyllotoxin and 5-fluorouracil because of possible teratogenic effects. Imiquimod is not approved for use in pregnancy as no data are available.
- Treatment is not always warranted but aims to minimise the number of lesions present at delivery and thereby to reduce the neonatal exposure to virus.
- Caesarean section is not indicated to prevent vertical transmission of HPV infection. The only serious, rare complication is recurrent respiratory papillomatosis in the infant, which occurs in about 4/100,000 births[50].
- Very rarely a caesarean section is indicated because of obstruction of the vaginal outlet with warts, or the presence of gross cervical warts.
- Cryotherapy, excision and ablative methods are safer options in pregnancy.

Breastfeeding

- Imiquimod: no quantifiable levels (>5 ng/ml) of Imiquimod are detected in the serum after single and multiple topical doses, however no specific advice is given in the summary of product characteristics on whether to use or not, in lactating mothers[51].
- Podophyllotoxin: there is insufficient information on the excretion of topically applied podophyllotoxin in human milk. A risk to breastfed infants cannot be excluded[52] and use is not recommended[53].

10.4.6 Warts in children and adolescents

Treatment of warts in children and adolescents follows the same principles as in adults, with the same range of treatment options, but is considered specifically in the BASHH guideline on children and young people[54].

10.4.7 Immunosuppressed

People with impaired cell mediated immunity, for example organ transplant recipients or those with HIV infection, experience lower response and increased relapse rates following treatment. Longer treatment courses may be required, and patients should be carefully followed-up, but no other modification of treatment recommendations is required.

11 Cervical cytology

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

12 Auditable outcome measures

The use of a treatment protocol has been shown to improve the management of genital warts.

It is recommended that a continuing audit cycle is adopted to ensure effective use of a protocol and for the incorporation of any new treatments available.

Recommended outcomes are:

- Adherence to a treatment algorithm (see Appendix for example) - 90% of patients.
- Percentage of patients with original wart clearance at 3 months - 60%.

Authors
Dr Richard Gilson (Consultant and Reader, University College London), Dr Mayura Nathan (Consultant in Genitourinary Medicine, Homerton Hospital, London), Dr Chris Sonnex (Consultant in Genitourinary Medicine, Addenbrookes Hospital, Cambridge), Dr Neil Lazaro (Associate Specialist in Genitourinary Medicine, Royal Preston Hospital, Preston), Tony Keirs (Sexual Health Nurse, Homerton Hospital, London)

The guidelines were reviewed and commented upon by members of the BASHH *HPV Special Interest Group* (S Bates, K Cuschieri, P Fox, P Goon, C Lacey, C O'Mahony, D Rowen, K Soldan, C Sonnex, N Steedman).

This guideline was commissioned and edited by the Clinical Effectiveness Group of the BASHH, without external funding being sought or obtained.

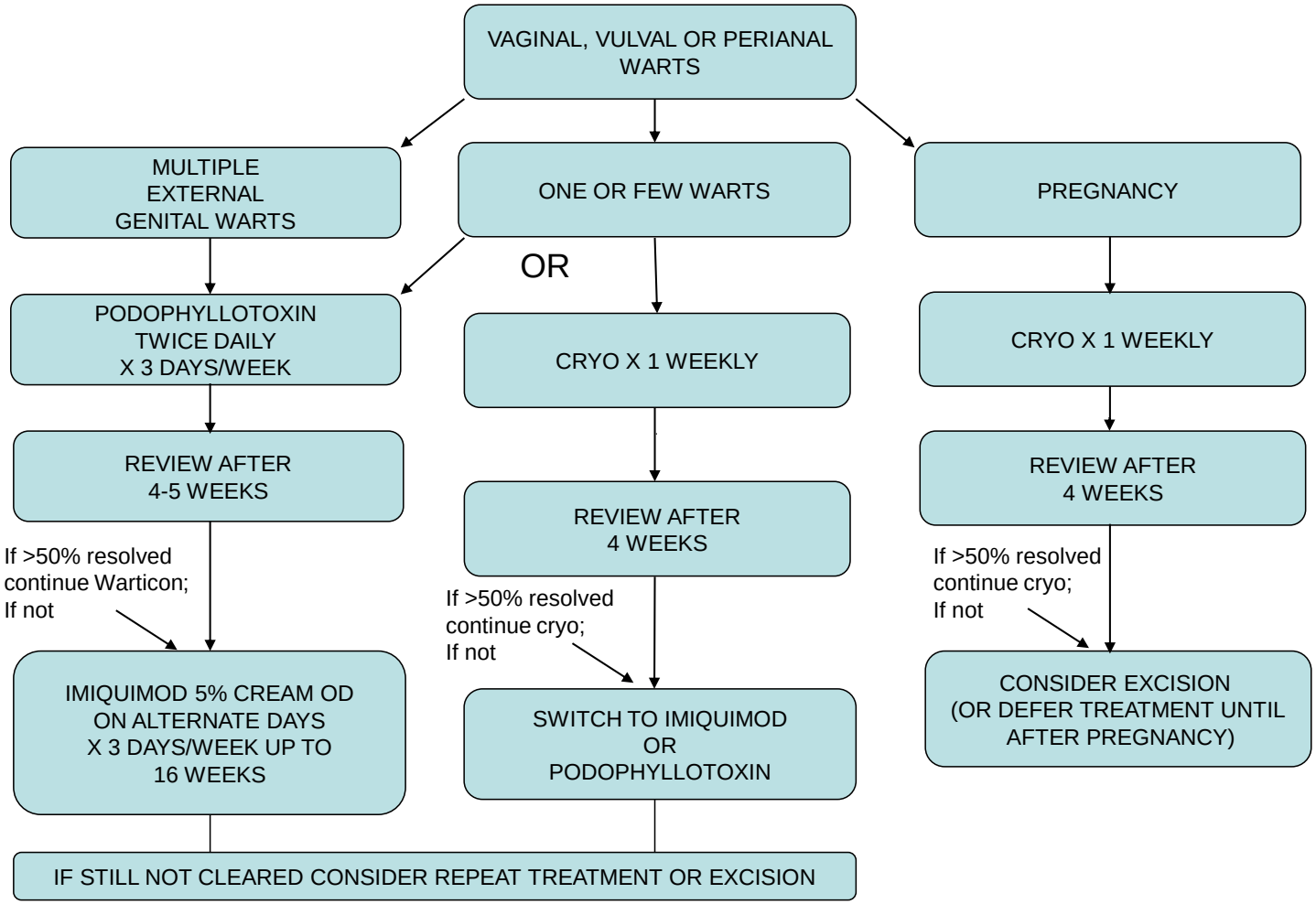
Acknowledgments
Comments were received from the following during the consultation period on the BASHH website: Georgina Keating, Claire McCausland, James Meek, Dr Ramalingam Nadarajah, Dr Colm O'Mahony, Dr Huw Price and Dr Conrad White

Potential conflicts of interest
Dr Fox has received sponsorship to attend scientific meetings and has participated in research sponsored by 3M Pharmaceuticals. Dr Nathan has conducted clinical trials for 3M Pharmaceuticals and has received sponsorship for attendance at scientific meetings. Dr D. Rowen has conducted clinical trials for 3M and Steifel. Dr Sonnex has conducted clinical trials for Stiefel and acted as an adviser to 3M pharmaceuticals. Dr Lacey has conducted clinical trials for Stiefel and acted as an adviser to 3M Pharmaceuticals. Dr Gilson has conducted clinical trials for Stiefel and 3M Pharmaceuticals.

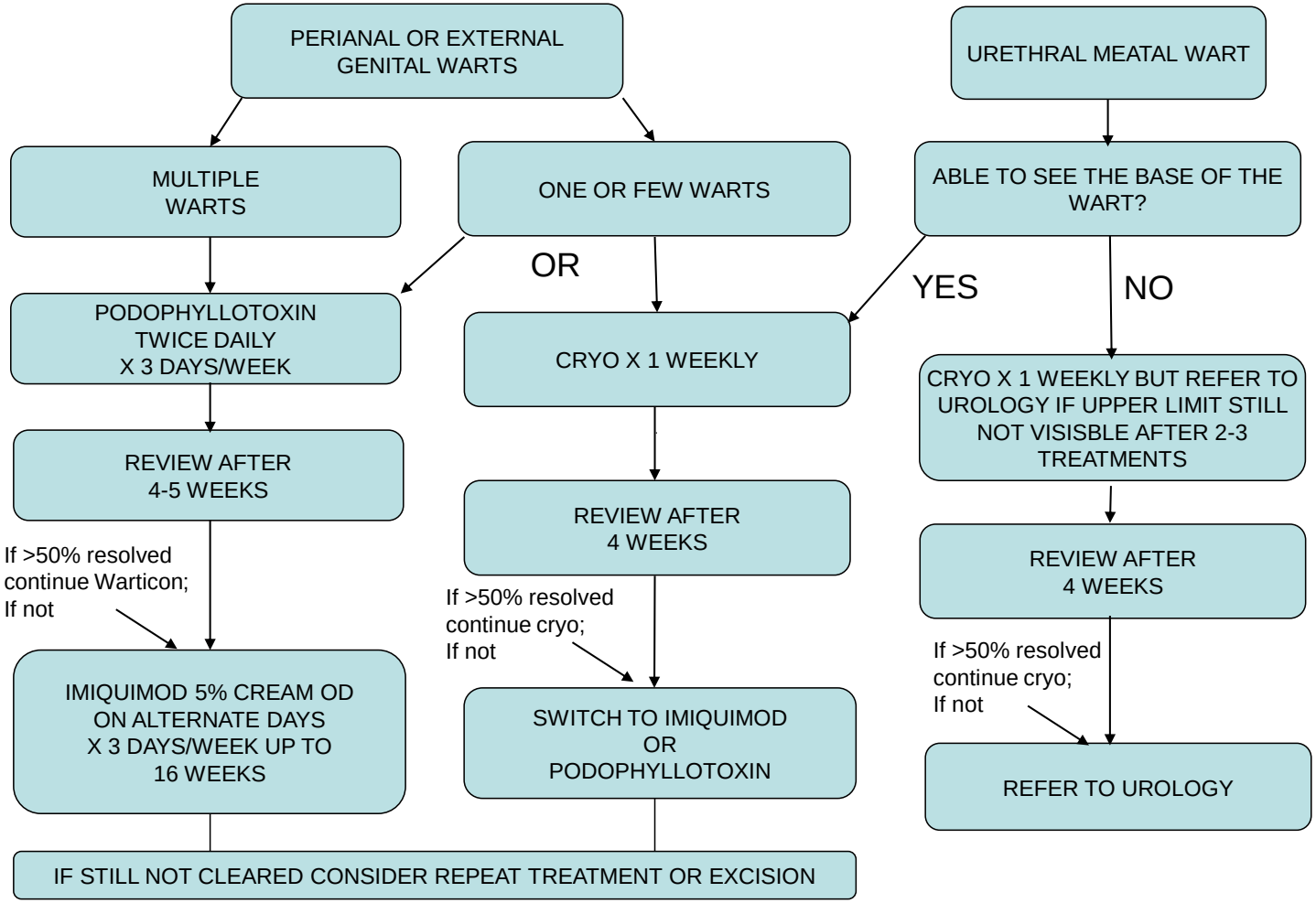
APPENDIX

The writing group has produced two suggested algorithms for the management of warts in males and females. Services may want to structure these differently for local use while still being consistent with the guidelines.

Flow-chart of management of warts in women



Flow-chart of management of warts in men



References

[1] Obalek S, Misiewicz J, Jablonska S, Favre M, Orth G. Childhood condyloma acuminatum: association with genital and cutaneous human papillomaviruses. Pediatr Dermatol.1993;10(2):101–106

[2] Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M, Franceschi S. Global burden of human papillomavirus and related diseases. Vaccine 2012; 30 Suppl 5: F12-23.

[3] Fairley CK, Hocking JS, Gurnin LC et al. Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination programme for young women. Sex Transm Infect 2009;85:499-502.

[4] Desai S, Wetten S, Woodhall SC et al. Genital warts and cost of care in England. Sex Transm Infect 2011;87:464-8.

[5] Rymark P, Forslund O, Hansson B-G, et al. Genital human papillomavirus infection is not a local but regional infection. Genitourin Med 1993;69:18-22.

[6] Oriel JD. Natural history of genital warts. Br J Vener Dis 1971;47:1-13.

[7] 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

[8] Arima Y. Winer RL. Feng Q. Hughes JP. Lee SK. Stern ME. O'Reilly SF. Koutsky LA. Development of genital warts after incident detection of human papillomavirus infection in young men. Journal of Infectious Diseases. 2010; 202(8):1181-4.

[9] Wen LM, Estcourt CS, Simpson JM, Mindel A. Risk factors for the acquisition of warts: are condoms protective? Sex Transm Inf 1999;75:312-6

[10] Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sex Transm Dis. 2002;29:725-35.

[11] Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, Koutsky LA. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med. 2006;354:2645-54

[12] Hogewoning CJ, Bleeker MC, van den Brule AJ, Voorhorst FJ, Snijders PJ, Berkhof J, Westenend PJ, Meijer CJ. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human

papillomavirus: a randomized clinical trial. Int J Cancer. 2003;107:811-6

[13] 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;107:804-10

[14] 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;92:1388-92

[15] Clarke P, Charles E, Cototti DN, Stewart S. The psychosocial impact of human papillomavirus infection: implications for health care providers. Int J STD AIDS 1996; 7: 197-200

[16] Wilson JD, Brown CB, Walker PP. Factors involved in clearance of genital warts. Int J STD & AIDS 2001;12:789-92

[17] Hippelainen MI, Hippelainen M, Saarikoski S, et al. Clinical course and prognostic factors of human papillomavirus infections in men. Sex Trans Dis 1994: 21(5): 272-279

[18] Pakianathan MR, Ross JDC, McMillan A. Characterizing patients with multiple sexually acquired infections: a multivariate analysis. Int J STD AIDS 1996;7:359-61.

[19] Eron LJ. Human papillomaviruses and anogenital disease. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. Infectious diseases. Philadelphia: WE Saunders, 1992: 952-6.

[20] Reynolds M, Fraser PA, Lacey CJN. Audits of the treatment of genital warts: closing the feedback loop. Int J STD AIDS 1996; 7: 347-52

[21] Lacey CJN, Woodhall SC, Wikstrom A, Ross J. 2012 European guideline for the management of anogenital warts. JEADV DOI: 10.1111/j.1468-3083.2012.04493.x

[22] Slade HB, Owens ML, Tomai MA et al. Imiquimod 5% cream (Aldara ™). Exp.Opin.Invest.Drugs 1998; 7(3): 437-449

[23] Gollnick HG, Barasso R, Jappe U, et al. Safety and efficacy of Imiquimod 5% cream in the treatment of penile warts in uncircumcised men when applied three times weekly or once per day. Int J STD AIDS. 2001; 12(1): 22-8.

[24] Edwards L, Ferenczy A, Eron L, et al. Self-administered Topical 5% Imiquimod Cream for external anogenital warts. Arch Dermatol 1998; 134:25-30

[25] Beutner KR, Tyring SK, Trofatter KF et al. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. Antimicrob. Agents Chemother 1998; 42 (4): 789-794.

[26] Kaspari M, Gutzmer R, Kaspari T, Kapp A, Brodersen JP. Application of imiquimod by suppositories (anal tampons) efficiently prevents recurrences after ablation of anal canal condyloma. Br J Dermatol. 2002;147(4):757-9.

[27] Carrasco D, vander Straten M, Tyring SK. Treatment of anogenital warts with imiquimod 5% cream followed by surgical excision of residual lesions. J Am Acad Dermatol. 2002;47(4 Suppl):S212-6.

[28] Fox PA, Nathan M, Francis N et al. A double blind randomised controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow data including the use of open label imiquimod. AIDS 2010;24: 2331-5.

[29] Mahto M, Nathan M, O'Mahony C. More than a decade on: review of the use of imiquimod in lower anogenital intraepithelial neoplasia. Int J STD AIDS 2010; 21: 8-16.

[30] Tatti S, Stockfleth E, Beutner KR et al. Polyphenon E: a new treatment for external anogenital warts. Br J Dermatol 2010;162:176-84.

[31] Batista CS, Atallah AN, Saconato H et al. 5-FU for genital warts in non-immunocompromised individuals. [Review] Cochrane Database of Systematic Reviews (4);CD006562,2010.

[32] Gross G, Roussaki A, Baur S, et al. Systematically administered interferon alfa-2a prevents recurrence of condylomata acuminata following CO2-laser ablation. The influence of the cyclic low-dose therapy regimen. Results of a multicentre double-blind placebo controlled clinical trial (letter). Genitourin Med 1996;72:71.

[33] Bonnez W, Oakes D, Choi A, et al. Therapeutic efficacy and complications of excisional biopsy of condyloma acuminatum. Sex Transm Dis 1996;23:273-6.

[34] Gross GE, Barrasso R. General principles of treatment. In: Gross GE, Barrasso R, eds. Human papillomavirus infection. A clinical atlas. Berlin: Ullstein Mosby, 1997:54-6.

[35] Ferenczy A. Laser therapy of genital condylomata acuminata. Obstet Gynecol 1984;63:703-7.

[36] Nathan M. Outpatient treatment of intrameatal warts in a genitourinary medicine department. Int J STD AIDS 1994;5:218-20.

[37] Nathan M, Hickey N, Mayuranathan L et al. Treatment of anal human papillomavirus disease – a long term outcome study. Int J STD AIDS 2008;19:445-9.

[38] Woodhall SC, Jit M, Soldan K et al. The impact of genital warts: loss of quality of life and cost of treatment in eight sexual health clinics in the UK. Sex Transm Infect 2011;87:458-463.

[39] 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;75:114-18.

[40] Wardropper A, Woolley P. Treatment of anogenital warts in genitourinary clinics in England and Wales. Int J STD AIDS 1992; 3: 439-41.

[41] Gilson RJ, Ross J, Maw R et al. A multicentre, randomised, double-blind, placebo controlled study of cryotherapy and podophyllotoxin cream as treatment for external anogenital warts. Sex Transm Inf 2009; 85:514-9.

[42] Gattai R, Torchia D, Salvini C et al. Photodynamic therapy for treatment of endoanal condylomata acuminate. Clin Infect Dis 2010;51:1222-3

[43] Friedman M, Bayer I, Letko I et al. Topical treatment for human papillomavirus-associated genital warts in humans with the novel tellurium immunomodulator AS101: assessment of its safety and efficacy. Br J Dermatol 2009;160:403-8.

[44] Marelli G, Papaleo E, Origoni M et al. Polyhexamethylene biguanide for treatment of external genital warts : a prospective, double-blind, randomized study. Eur Rev Med Pharmacol Sci. 2005; 9(6): 369-72.

[45] Langley PC, Richwald GA, Smith MH Modeling the impact of treatment options in genital warts: patient-applied versusphysician-administered therapies. Clinical Therapeutics 1999; 21: 2143-55

[46] Williams P, von Krogh G. The cost-effectiveness of patient-applied treatments for anogenital warts. Int J STD AIDS 2003; 14: 228

[47] Lacey CJ. Goodall RL. Tennvall GR. Maw R. Kinghorn GR. Fisk PG. Barton S. Byren I. Perstop Pharma Genital Warts Clinical Trial Group. Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. Sexually Transmitted Infections 2003; 79: 270-5.

[48] Carey FM, Quah SP, Dinsmore W, Maw RD. Patient assessment of anogenital warts and the success of treatment with home applied therapy.

Int J STD & AIDS 2004;15:316-8

[49] Colposcopy and Programme Management: Guidelines for the NHS Cervical Screening Programme. NHSCSP Publication No 20, May 2010

[50] Lacour DE. Trimble C. Human papillomavirus in infants: transmission, prevalence, and persistence. Journal of Pediatric & Adolescent Gynecology. 2012; 25: 93-7

[51] Aldara® 5% cream: Summary of Product Characteristics datasheet 24.6.2010 Meda Pharmaceuticals. Available at http://www.medicines.org.uk/emc/medicine/8/SPC/Aldara+5++Cream/#PREGNANCY (accessed 28.9.2015)

[52] Warticon® cream : Summary of Product Characteristics datasheet 12.7.2013 Stiefel . Available at http://www.medicines.org.uk/emc/medicine/7322/SPC/Warticon+Cream/#PREGNANCY (accessed 28.9.2015)

[53] Condyline® cutaneous solution: Summary of Product Characteristics datasheet 18.4.2013 Takeda UK Ltd. Available at http://www.medicines.org.uk/emc/medicine/22861/SPC/Condyline/#PREGNANCY (accessed 28.9.2015)

[54] Rogstad K, Thomas A, Williams O, Forster G, Munday P, Robinson A, Rooney G, Sherrard J, Tenant-Flowers M, Wilkinson D, Lazaro N, on behalf of Clinical Effectiveness Group, British Association for Sexual Health and HIV. United Kingdom National Guideline on the Management of Sexually Transmitted Infections and Related Conditions in Children and Young People – 2010 http://www.bashh.org/documents/2674.pdf