# Frequently asked questions about genital warts in the genitourinary medicine clinic: an update and review of recent literature

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## ABSTRACT

Genital warts are the commonest viral STI in the UK, and the incidence continues to rise. Diagnosing, treating and advising patients about this infection remain a large part of the work in any department of GU Medicine. This article reviews and provides the levels of evidence currently available on data about genital warts, and is primarily to advise and guide clinicians when faced with commonly asked questions in the clinic.

Evidence-based medicine is now de rigueur for all fields of medicine, and genitourinary medicine in the UK is no exception. Advice to patients in the clinic can vary from person to person and from centre to centre. This depends entirely on the knowledge base upon which the answers are formulated. The diagnosis of primary genital warts often causes psychological distress, and there are likely to be some difficult questions posed to the healthcare professional. Inaccurate or inadequate advice at the time of presentation or follow-up is likely to compound these problems. Although a review of appropriate information for patients with genital warts has been previously published,[1] this appeared some years ago, and more recent studies suggest that an update is warranted. In this article, we summarise the evidence and answers to date for some of the most commonly encountered questions in the clinic.

## METHODS

### Search strategy

We have undertaken a search of Medline/PubMed and Cochrane databases up until December 2006 using MeSH headings "human papillomavirus", "genital warts", "anogenital warts", "treatment", "HPV", "condoms", "laryngeal papillomatosis" and "smoking" as single or combined keywords.

Of 1537 non-duplicate abstracts identified, 93 were deemed eligible for full text searching. Exclusion criteria included ineligibility, insufficient focus, insufficient information and overlapping study populations. Six further papers were identified by peer review and communication. Sixty-eight papers were deemed important to the exposition of the paper.

In compiling this review of current evidence, we have used grades of evidence as given below. It is evident that there is an occasional lack of clear clinical trial data, and so we have attempted to collate and summarise the main clinical findings from available studies. The levels of evidence (LOE) have been graded as shown below and adapted from Wright *et al*:[2]

- 1a, evidence obtained from meta-analysis of randomised controlled trials
- 1b, evidence obtained from at least one randomised controlled trial
- 2a, evidence obtained from at least one well-designed controlled study without randomisation
- 2b, evidence obtained from at least one other type of well-designed quasi-experimental study
- 3, evidence obtained from well-designed non-experimental descriptive studies
- 4, evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

## RESULTS

### What causes genital warts?

Human papillomavirus (HPV) is the causative agent of genital warts. Over 40 HPV types infect the genital tract. HPV types 6 and 11 (low-oncogenic-risk (LR) types) cause the vast majority of genital warts (90%), although some are co-infected with high-oncogenic-risk (HR) types[3 4] (LOE—2a). Using a novel polymerase chain reaction and reverse blot strip assay, Brown *et al* identified multiple HPV types in 56% of genital warts excised from immunocompetent patients.[4] Of these multiply infected lesions, HR HPV types were identified in 86%, HPV 16 being the most common type detected. HR type co-infection has been confirmed by a more recent study which documented HPV 16/18 in 11% of genital warts[5] (LOE—2a).

In contrast to LR infection, HR types usually cause sub-clinical or latent infections. Some of these HR type lesions may be identified by whitening of the epithelium after the application of acetic acid, so called "aceto-whitening"[6 7] (LOE—2a). Therefore, when answering patient queries along these lines, it should be strongly emphasised that HPV 6 and 11 cause the vast majority of visible genital warts.

### Are genital warts always sexually transmitted?

There is strong evidence for transmission through sexual contact[8] (LOE—3). There is little evidence for auto-inoculation of the virus,[8–10] although case reports and analyses of genital wart data in children suggest that hand-to-genital transmission may occur.[11 12] In addition, genital HPV has been detected in virginal women, which suggested to the authors transmission by non-penetrative sexual

contact.[13] Although uncommon, these other potential routes of viral transmission should be considered when counselling patients.

Similarly, although HPV DNA has been found on inanimate objects, there is no evidence that transmission of virus can occur this way (fomites).[14 15]

A number of studies have reported an association between oral HPV infection and oral sex,[16–19] although one study found no association.[20] One case-control study has also reported a strong link between oral sex and oral cancer.[21] It would therefore seem appropriate to inform patients with genital warts of the potential risk of HPV transmission to the mouth by oral sex (LOE—2a). There is currently no evidence to suggest that treatments affect the duration of HPV shedding and therefore the transmission risk.

### I've heard that the wart virus causes cancer, is this true?

It should be emphasised that the LR HPV types associated with clinical wart disease do not cause cancer (LOE—3). The likely reason for this is the lack of transformation activity of LR E6 and E7 as documented in in vitro transformation assays.[22 23] However, in very exceptional circumstances, such as the Buschke–Lowenstein tumours, the LR types may induce massive tissue growth with subsequent occasional dysplastic change.[24 25] The HR HPV types specifically associated with high-grade squamous intraepithelial lesions (SIL) and cervical and other genital carcinomas do not cause warts (as mentioned above). So, although patients can be reassured that the HPV types that cause genital warts do not cause cancer, the answer to the question "am I more likely to develop ano-genital cancer if I have genital warts?" is rather different. A Danish study has reported an increased risk of ano-genital neoplasia, particularly vulvar cancer, in women hospitalised for the management of their genital warts. Of the cohort of 9552 women, 11 cases of vulvar cancer were identified, with 0.3 expected (standardised incidence ratio [SIR], 40.1; 95% confidence interval [CI], 20.0 to 71.7), and there were increased risks for cervical cancer (SIR, 2.0; 95% CI, 1.3 to 3.0), anal cancer (SIR, 8.5; 95% CI, 0.9 to 30.5), and CIN III (SIR, 2.6; 95% CI, 2.3 to 2.9).[26] Similarly, a more recent and much larger study from Sweden reporting on 1685 men and 9286 women hospitalised with genital warts identified elevated risks for cancers of the vulva (n = 13, SIR = 10.2, 95% confidence interval (CI) = 5.4 to 17.4), vagina (n = 4, SIR = 12.0, 95% CI = 3.3 to 30.7) and penis (n = 5, SIR = 21.9, 95% CI = 7.1 to 51.2). There was a moderate excess risk of cervical cancer in situ (n = 259, SIR = 1.9, 95% CI = 1.7 to 2.1), but not invasive cervical cancer.[27] In view of the typically slow progression from initial HPV infection to the development of high-grade SIL and carcinoma,[28 29] women with genital warts can be reassured that they do not require more frequent cervical screening and should adhere to their screening programme. However, it would be prudent to advise all patients with ano-genital warts to present early if they develop future ano-genital lesions or anal bleeding (LOE—3).

### How long does it take for the warts to go?

Appropriate treatment generally clears most warts within 3 months[30] (LOE—2a). It is a matter of debate currently whether this "clearance" means that there is still residual virus which is not active (latent) or that all virus has been completely eradicated from the body. Destructive methods such as diathermy, laser ablation and excision will have an immediate effect, as lesions may be removed in one clinic visit. However, these treatment methods require the use of local anaesthetic which, even with the prior application of prilocaine/lignocaine cream, is uncomfortable for many patients. Wart burden at presentation is a good indicator of time to clearance, with the number of warts present being the best indicator. Patients with 1–3 warts have been reported to require significantly fewer treatment episodes than those with more lesions.[31] Interestingly, a high HPV load has been reported to be associated with duration, extent of disease, persistence and likelihood of recurrence,[5 32] although this is of limited relevance when counselling patients.

The institution of treatment algorithms has been found to be helpful as these advocate systematic treatment as well as treatment change in the event of partial or non-response. It was found that 6 months after these guidelines were adopted, there were significant decreases in the numbers of patients still requiring treatment at 3 months (men 44% to 8%; women 38% to 3%).[30]

### Will the wart virus stay with me, and if so, will I be infectious?

Although it is generally thought that the vast majority of people infected with HPV do not develop clinically apparent warts,[33 34] Winer *et al* recently reported that 60% of women with incident HPV 6/11 infection develop lesions within 2 years of infection.[35] We also appreciate that patients with genital warts frequently have areas of genital epithelium subclinically infected with HPV.[36] Ferenczy *et al* reported that 45% of patients with genital warts had detectable HPV in the surrounding normal appearing epithelium and that these patients were more likely to have recurrences after treatment.[37]

Data on HPV persistence have been from studies looking at HPV DNA in subclinical infection, and there are few data on those with visible warts.

The consensus definition of "persistence" is also not clear. Most studies have termed HPV infection as persistent if HPV DNA was detected on two consecutive visits, usually 4–6 months apart. However, there are many potentially confounding factors such as the follow-up interval, which varies between studies, viral latency (rendering virus undetectable for an unknown period of time but then re-emerging), re-infection rates, and so on, which cause problems in the interpretation of data. Despite this, there is evidence suggesting that the median duration of HPV DNA detectability is approximately 1 year. In a prospective study of female students with cervico-vaginal HPV infection, ~70% of women were HPV DNA undetectable ("cleared") at 12 months after incident HPV infection and over 80% at 18 months.[38] Although there is some controversy about whether HR- and LR-type associated lesions persist for similar periods, some studies have suggested a longer persistence for HR types, in particular HPV 16.[38 39] It is uncertain whether the natural history of genital warts containing multiple HPV types differs from those with single HPV 6 or 11 infection, although recurrence has been reported to be more common.[5] A higher viral load has been reported to be associated with wart persistence[32] and recurrence,[5] but possibly of limited relevance when counselling patients. Regarding infectivity, although HPV DNA viral load does increase from the latent to the sub-clinical to the clinically overt state, the exact infectivity of each state is unclear.[8 40] So, although we can tell patients they are potentially more infectious when warts are present, their relative degree of infectivity with purely subclinical infection is not known (LOE—3). Similarly, although wart treatment reduces tissue load and therefore, potentially, viral load, there is no evidence to date that this reduces the risk of HPV transmission nor the development of disease in the sexual partner.

### I am pregnant. How will warts affect me or my child?

Genital warts may increase in number, size, or recur during pregnancy.[8 41] Vertical transmission in utero is extremely rare, and the mechanism is unclear.[42] There are more data about the possibility of passing the virus on to the neonate via vaginal delivery.[43 44] Transmission has been estimated to be between 1:80 and 1:1500.[44] The most important manifestation of mother-to-child transmission of wart virus is juvenile laryngeal papillomatosis. This disease appears to be associated with maternal genital warts at the time of delivery. In one study, 54% of a group of children with juvenile laryngeal papillomatosis had a maternal history of vulval warts at time of delivery.[45] The incidence of recurrent respiratory papillomatosis among children is estimated at 4.3 per 100 000 and 1.8 per 100 000 among adults.[46] Although an important disease with significant morbidity (patients may require multiple operative treatments to manage their disease), the lesions are histologically benign but can occasionally progress in the presence of other environmental factors (such as smoking) to malignancy. It is therefore important to stress that vertical transmission is rare and almost always occurs via vaginal delivery with obvious maternal warts at that time. Although the patient may wish to discuss the option of a caesarean section, this is not generally recommended, unless warts obstruct the vagina or cause extensive cervical disease (LOE—3). Visible warts can be treated with cryotherapy, trichloracetic acid or excision during the pregnancy, although "no treatment" is a reasonable option as warts usually spontaneously regress after delivery. Podophyllin or podophyllotoxin is contra-indicated during pregnancy or conception due to potential teratogenic effects.[47]

### Does condom use help prevent transmission or re-infection?

The variability of advice given by GU consultants has been documented.[48] A large proportion of HPV disease is sub-clinical, and because ano-genital HPV infection is usually multi-centric, the use of ablative therapies on macroscopically infected tissue is unlikely to effect complete eradication of infection. Studies have suggested that clinical disease is more infectious than sub-clinical and that the infectivity of HPV is associated with the detectable HPV viral load.[8 40] However, it is still likely that the long incubation period before the appearance of clinically visible warts (median of 3 months with HPV 6 and 11 infection[35]) will allow some transmission of infection to sexual partners. Considering the medical literature, Wen *et al* found a protective effect of condoms in reducing the risk of acquiring genital warts[49] and similarly a meta-analysis of 20 published studies found that condoms provided no protection against HPV acquisition, but they may offer some protection against genital warts, high-grade CIN and cervical cancer.[50] In contrast to this, a recent study has shown that among newly sexually active women, consistent condom use by their partners appears to reduce the risk of cervical and vulvo-vaginal HPV infection.[51] Other studies have documented that condom use leads to a shorter median time to regression of penile HPV lesions in male contacts of women with CIN, possibly by preventing re-infection from the female partner.[52 53] Condom use has also been found to produce higher rates of cervical HPV clearance and CIN regression.[54] Although data are somewhat conflicting, it should be stressed that condoms may protect against HPV acquisition, particularly when used consistently, and also have a therapeutic effect when both partners are infected, possibly by preventing continued re-exposure to the virus (LOE—2b). These are new findings and will inevitably require confirmation.

### Will I get a recurrence of warts once I have cleared my infection?

Since HPV infection is typically multi-centric, the recurrence rates with currently recommended treatments can be high and range from about 10% to 90%. We refer the reader to a comprehensive review of treatments for genital warts.[55] Of the treatments available today, only one acts via activation of the immune response, and this then clears the infection. Consequently, the recurrence rate for Imiquimod has been shown to be lower than for the other (ablative) treatments.[55] It is possible that other immune modulators encouraging immune clearance will be available in the future.

### Why do people who do not have anal sex sometimes get anal warts?

This can be a major source of embarrassment for some clinic attendees who deny ever having anal intercourse. They should be reassured that anal warts have been reported to commonly occur in the absence of anal intercourse[56] (LOE—3). This is presumed to happen because HPV is typically a multi-centric infection, and infection may not be limited to the initial site of inoculation. Although the transfer of HPV by fingers from the genital to anal epithelium during foreplay remains a possible explanation for some patients, this route of transmission has not been confirmed.[57]

### Would HPV vaccination prevent further recurrences of genital warts?

Two HPV vaccines are presently available, and both are prophylactic rather than therapeutic. A quadrivalent L1 virus like particle vaccine ("Gardasil"™) protects against HPV types 6, 11, 16 and 18, and has been shown to be effective in preventing the acquisition of genital warts in a modified intent-to-treat cohort.[58] This vaccine is now licensed in the UK, and vaccination has been recommended for 12–13-year-old girls as part of the childhood vaccination schedule. Although there are no published data on patients with previous genital warts, it is possible that boosting type specific antibodies to HPV types 6 and 11 may provide protection against re-infection. However, this could prove insufficient to prevent recurrences, which is likely to require a host-cell-mediated immune response against the virus.

### Should I or my partner get an "HPV test"?

HPV testing is commercially available and involves detecting HPV DNA by a nucleic acid amplification test from either self-obtained or practitioner-obtained genital swabs. The role of HPV testing is yet to be defined, but a case could be made for testing for high-risk HPV types in women with borderline or mildly dysplastic changes on cervical cytology, as an adjunct to cervical cytology in women over the age of 35 and in women post-treatment for cervical intraepithelial neoplasia (CIN).[59 60] Routine HPV testing is currently not recommended in view of the transient nature of the majority of infection and the potential for a high-risk HPV type positive result to cause undue anxiety. As mentioned previously, the detection of subclinical non-cervical HPV infection is of uncertain relevance with respect to both the likelihood of disease development and infectivity.

### Can I do anything to help clear the warts or prevent getting a recurrence?

There are limited published studies looking specifically at the effect of lifestyle, psychological well-being or diet on the natural history of genital HPV infection. Excessive alcohol intake, but

## Key messages

- Sexual transmission of genital warts, including oral sex, is the most common route of infection
- Consistent condom use has been shown to reduce the acquisition of HPV
- An HPV vaccine is now licensed in the UK, and the Joint Committee on Vaccination and Immunisation have recommended vaccination of 12–13-year-old girls as part of the childhood vaccination schedule
- Women should continue to undergo cervical screening despite the availability of this vaccine

not vitamin A and C consumption, has been reported to increase the risk of developing genital warts.[61] There are a number of studies reporting an association between chronic stress and depression with decreased cell-mediated immune function, including natural-killer-cell activity.[62 63] The advice to try to reduce stress and lead a "healthy lifestyle" would appear sound and partially supported by clinical evidence (LOE—2b), but there are no studies looking specifically at these issues in patients with genital warts.

Studies examining the interaction between smoking and HPV infection have produced conflicting data. Wilson *et al* reported higher wart clearance rates in non-smokers, although this failed to reach statistical significance,[31] a similar result to that previously reported in men with genital warts.[64] Data on the association between smoking and developing genital warts or acquiring HPV infection are also conflicting, with some studies reporting an increased risk[13 65] and others failing to find an association.[66] In HIV-infected women, smoking has been found to be associated with an increased incidence and prevalence of genital HPV infection.[67] There is perhaps more concern for women smokers with cervical HPV infection who appear to be at greater risk of developing cervical low-grade SIL than non-smokers.[68] On current evidence, we therefore feel it is prudent to advise patients with genital HPV infection to reduce or stop smoking (LOE—3).

In conclusion, knowledge of genital HPV infection continues to expand and although a number of management and patient guidance related issues (eg, HPV infectivity and optimal treatment) require further study, we have attempted to produce an up-to-date information summary for practitioners treating patients with ano-genital warts.

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# Frequently asked questions about genital warts in the genitourinary medicine clinic: an update and review of recent literature

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