Journal of Infection and Chemotherapy xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Guideline

Asian guidelines for condyloma acuminatum

Tekumalla Sindhuja, Neetu Bhari, Somesh Gupta *

Department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi, India

ARTICLE INFO

Keywords:
Condyloma acuminata
Anal wart
Anogenital wart
Genital wart
Genital HPV

EXECUTIVE SUMMARY

The present guidelines aim to provide comprehensive information on genital condyloma acuminata, including the epidemiology, clinical features, diagnosis and management. The guidelines provide evidence-based recommendations on the diagnosis, prevention and treatment of genital condyloma acuminata in adults in Asia, including patients with HIV co-infection.

Methodology: A PubMed search was performed, using the keywords "condyloma acuminata", "anal wart", "anogenital wart", "genital wart" and "genital HPV". A total of 3031 results were found in publications during last six years. A careful review of the titles and abstracts was done to find all the studies pertaining to epidemiology, clinical features, diagnosis, treatment and prevention of condyloma acuminata.

Diagnosis: Various diagnostic procedures described are:

1. PCR (LE: 2b).
2. Serology (LE: 2b).
3. In-situ hybridization (LE: 3).

Prevention: 1. Vaccination (LE: 1a): Quadrivalent vaccine reduced the frequency of anogenital warts in both vaccinated and unvaccinated contacts.

According to the update Advisory Committee on Immunization Practices (ACIP) recommendations, the following protocol is recommended:

(a). HPV vaccination at age 11 or 12 years for both males and females.
(b). Catch-up vaccination for all persons through age 26 years.
(c). Shared clinical decision-making regarding potential HPV vaccination for persons aged 27–45 years, who are at risk of new HPV infection.

2. Male circumcision (LE: 2a): conflicting evidence.

HIV and condyloma acuminata: In HIV-affected individuals, the course of HPV is more aggressive, with a greater risk of treatment resistance, increased chances of intraepithelial neoplasia as well as cancers.

Treatment: Physician administered.

1. Photodynamic therapy (LE: 1a).
2. Laser (LE: 2b).
3. Surgery (LE: 1a).
4. Electrosurgery (LE: 2c).
5. Cryotherapy (LE: 1b).
6. Immunotherapy (LE: 1b).
7. Podophyllin (LE: 1b).

Provider administered.

1. Imiquimod 5%(LE: 1a).
2. Podophyllotoxin (LE: 1b).
3. Sinecatechins (LE: 1a).
4. Cidofovir (LE: 3).
5. 5- Fluorouracil (LE: 1a).
6. Interferon (LE: 1a).

Abbreviations: HPV, Human papilloma virus; CIN, Cervical intraepithelial neoplasia; MSM, Men who have sex with men; HIV, Human immunodeficiency virus; ACIP, Advisory Committee on Immunization Practices; LE, Level of evidence.

* Corresponding author.
E-mail address: someshgupta@hotmail.com (S. Gupta).

https://doi.org/10.1016/j.jiac.2022.03.004
Received 5 December 2021; Received in revised form 16 February 2022; Accepted 8 March 2022

1. Introduction

Human papilloma virus (HPV) is the most common sexually transmitted disease in the world. Almost 80% of the world's population is exposed by the age of 50 years. It is the most common sexually transmitted infection, with the probability of infection exceeding 80% for women and 90% for males across their lifetime [1]. Genital HPV infection can be divided into low-risk infections (causing anogenital warts) and high-risk infections (causing cervical intraepithelial neoplasia (CIN), and cervical, oropharyngeal and anal cancers) [2].

HPV infections most commonly affect young adults, females being more commonly affected than males. Over a 100 HPV types have been identified, with HPV types 6 and 11 being responsible for approximately 90% of genital warts, and HPV types 16 and 18 for 70% of invasive cervical cancers. Apart from the inconvenience and discomfort of treatment, genital warts inflict substantial psychosocial burden due to the fear of recurrence, transmission, and the possible threat of cancer. Patients are also burdened by the shame and embarrassment related to the diagnosis of genital warts. Costs related to routine screening for cervical cancer, treatment of genital warts, and the management and follow-up of malignancies lead to substantial economic burden [3].

In the US, prevalence of anogenital warts decreased during 2008–2014 among females aged 15–19 years (annual percentage change [APC] −14.1%; $P < 0.001$); and during 2009–2014 among men and women aged 20–24 years (APC -6.5%; $P = 0.005$ and −12.9%; $P < 0.001$) and among women aged 25–29 years (APC -6.0%; $P = 0.001$) [4]. Enough data on incidence of new cases is not available for Asia. In Connecticut, which achieved a moderate uptake of HPV vaccine in 2013, the overall proportion of incident anogenital warts diagnoses decreased by 64.5% within the 5-year (2013–2017) study period (from 3.1 cases per 1000 visits to 1.1 cases per 1000 visits; incident rate ratio, 0.36; 95% confidence interval [CI] 0.18 to 0.70; $P = 0.003$) [5].

2. Epidemiology

Analysis of the Korean health insurance review and assessment data revealed that the overall prevalence and socio-economic burden of anogenital warts has increased during the years 2007–2015 [average annual percent change (APC) of +8·3%]. However, the female prevalence increased until 2012, and decreased thereafter (APC +3·6%), after the introduction of routine HPV vaccination for females. The male prevalence increased continuously over time (APC +11·6%), especially in those aged 20–49 years [3]. The estimated number of newly diagnosed cases of condyloma acuminatum per 100,000 population in 2015 in Japan was 61 (95% CI 29–93) [6].

Overall prevalence of genital warts among 44061 patients ages 18–60 years examined by 200 physicians across six cities in India in 2011, was estimated at 1.07% (95% CI 0.97–1.17) and was higher among men than women. Regional prevalence ranged from high in Delhi (2.17%) to low in Bangalore (0.40%) and patients aged 25–29 years had the highest prevalence (1.42%). Patients with genital warts were most often newly diagnosed (74.07%). Among those with existing genital warts, 56.24% were recurrent, and 43.76% were resistant [7]. A similar overall prevalence of genital warts (1.1%) was observed in Taiwan from October 2011 to May 2012 among those seeking healthcare, with a higher prevalence among men [8]. Among patients seeking healthcare between July and September 2011 in Korea, the estimated overall prevalence of genital warts was 0.7% (95% CI 0.7%–0.8%); 0.6% (95% CI 0.6%–0.7%) among women, and 1.0% (95% CI 0.9%–1.0%) among men, with a peak around 18–24 years [9].

According to a prospective hospital-based study conducted in China from September 2014 to April 2017 including 879 patients with genital warts, the detectable rates of low-risk, high-risk and total HPV types were 45.4%, 34.5% and 57.8%, respectively. The detectable rate of low-risk HPV types (45.4%) was significantly higher than that of high-risk HPV types (34.5%) ($\chi2 = 21.85$, $p < 0.01$). The detectable rate of low-risk HPV types in men (52.3%) was significantly higher than that in women (35.7%) ($\chi2 = 23.90$, $p < 0.01$). The detectable rates of one, two, and three or more HPV type infections or coinfections were 26.1%, 17.5% and 14.2%, respectively. HPV6 (24.9%), HPV11 (17.9%), HPV52 (9.9%) and HPV16 (7.3%) were the four most common HPV types [10]. Among Thai patients with anogenital warts, HPV was identified in 88.3% (182/206) of the samples and the majority were of low-risk genotypes- HPV6 (36.9%) and HPV11 (36.4%) [11].

2.1. Special population groups

Men who have sex with men (MSM) living with human immunodeficiency virus (HIV) and anogenital warts are at disproportionate risk for high risk HPV. In a cross-sectional study in Taiwan during 2013–2016 including 279 MSM aged 20 years or older, HIV-infected subjects had a significantly higher prevalence of high risk HPV infection (adjusted odds ratio [OR], 5.80; 95% CI 2.57–13.11), compared to HIV-uninfected subjects [12]. According to a systematic review and meta-analysis, the estimated prevalence of anal HPV among MSM in China was 85.1% (HIV-positive), 53.6% (HIV-negative), and 59.2% (unknown HIV status), with HPV genotypes being predominated by HPV 6, 11, 16, 18, 52, and 58 [13].

The infection rates of condyloma acuminatum among pregnant women in Japan in 2015 was 1/444 (225 in 100,000). The rates of infection in teenaged pregnant women were higher than those in women aged ≥20 years ($p < 0.01$) and infection rates in women aged 20–29 years were higher than those aged ≥30 years ($p < 0.01$) [14].

3. Risk factors

Risk factors for persistent HPV infection include multiple sex partners, sex at an early age, history of sexually transmitted infections, and smoking [15].

4. Transmission

Transmission occurs by way of skin-to-skin contact through sexual intercourse, oral sex, anal sex, or other contact involving the genital area. Transmission may also occur through fomites and gynecological equipment like ultrasound probes [16]. The virus may remain latent for months to years until a trigger causes replication of the viral DNA, leading to clinical manifestation of anogenital warts. There is a definite risk of viral transmission to asymptomatic partners in HPV infection, as HPV DNA was detected in 34.5% of asymptomatic male partners of infected women. Thus, partner protection should be recommended to minimize the viral transmission [17]. (LE: 2b).

5. Clinical features

Low-risk HPV such as HPV-6 and 11 commonly present as asymptomatic infections in men and women [18]. The prevalence of genital HPV infection was 65.2% in asymptomatic males aged 18–70 years [19]. In individuals presenting with genital HPV lesions, more than 90% of genital warts are caused by non-oncogenic HPV types 6 and 11 [19]. External genital warts occur at multiple sites in nearly 50% of patients and typically appear in anogenital areas, such as the vulva, penis, groin, perineum, perianal skin, or mucosal surfaces. The genital HPV infections can be clinically evident at one site and may remain dormant at other [20].

The four main morphological types of genital warts are condylomatous, keratotic, papular, and flat. Papular warts are skin-colored, dome-shaped papules of 1- to 4-mm size, that occur only on the fully keratinized skin. Flat warts can occur on the fully keratinized skin or moist skin and are macules or barely elevated papules. Keratotic warts have thick horny layer and are seen only on the fully keratinized skin. Condylomatous warts are cauliflower shaped lesions, seen on the moist

surfaces. Anogenital warts may also be accompanied by symptoms such as pruritus, burning, pain, and obstruction [21].

Patients with anal condyloma acuminata may be asymptomatic or present with painless papules, itching, and discharge or bleeding per rectum. It is not uncommon to have more than one involved area; multiple lesions may be present and extend into the anal canal or rectum [22]. Various studies support the importance of an exhaustive proctological examination in patients suffering from condylomatosis of the anogenital area, as it was found that out of 362 patients with both endoanal and perianal condyloma, only half of them were detectable by perianal clinical examination [23]. It was found that multiple HPV infections predisposed an individual to more warts, larger warts, a longer disease course, and a greater frequency of recurrences. The cases infected with the high-risk type, HPV16, accounted for 60% of the multiple infections and had a higher relapse rate than any other type of HPV infection [24].

HPV-associated intermediate malignant or premalignant conditions include giant condyloma acuminata (also called Buschke-Lowenstein tumor), anal, penile and vaginal or vulvar intraepithelial neoplasia while frankly malignant diseases include invasive anal, penile, or vulvar carcinoma. In HIV-infected individuals, the course of HPV is more aggressive; there is higher risk of treatment-resistance and increased chances of intraepithelial neoplasia and cancers [25].

6. Diagnosis

Most condylomata are diagnosed clinically on the basis of their characteristic morphology and location. Investigations for diagnosis and management are needed only in a small proportion of cases. Extensive investigations to detect asymptomatic infection may not be required; as it has now been proven that HPV infection is transient with a median duration of 7.52 months (6.80–8.61) for any HPV and 12.19 months (7.16–18.17) for HPV 16 [18], with only 9% of the infection persisting after 24 months [26].

6.1. Histopathology

Biopsy is indicated in the case of atypical lesions, lesions with doubtful diagnosis, larger lesions, lesions that are not responsive to therapy and in immunocompromised patients. In immunohistochemistry, P16 staining is found to be useful in differentiating condyloma acuminata from bowenoid papulosis. In a study by Kazlouskaya et al., 36 skin biopsy specimens (24 samples of condyloma and 12 of bowenoid papulosis) were stained with an antibody to p16 protein and all cases of bowenoid papulosis showed diffuse staining while 75% of condyloma lesions showed sporadic and focal positive staining for p16 protein [27]. (LE: 3) In addition, p16 has been shown to be a surrogate marker of infection by high-risk HPV. It has proven benefit in distinguishing high-grade cervical dysplasia from benign conditions like cervical atrophy, reactive inflammatory lesions, and low-risk HPV infections which show weak expression of p16. In combination with additional markers like Ki-67, it can help distinguish low and high-grade CIN [28]. Ki-67 is a reliable marker to pathologically distinguish anogenital warts from benign vulvar vestibular papules in women, and pearly penile papules in men [29]. (LE: 3B).

6.2. Polymerase chain reaction

HPV L1 sequencing and type-specific HPV-6, 11, 16, and 18 real-time polymerase chain reaction (PCR) for identification and typing of HPV can be done; however, this test is useful only for research settings and does not have much diagnostic or prognostic value [30]. (LE: 2b) Laser capture microdissection-polymerase chain reaction (LCM-PCR) is more precise than whole-tissue section in assigning individual genotypes to specific lesions. LCM-PCR supported by p16 was used to demonstrate HPV deoxyribonucleic acid (DNA) in condylomas, which are most commonly associated with HPV-11 genotype [31].

6.3. In-situ hybridization

Rarely, in some cases, additional confirmation of HPV infection or typing maybe desired, where in-situ hybridization (ISH) test maybe useful. It can detect a very low copy number of HPV DNA sequences in paraffin-embedded tissue sections. In a study, 210 cervical tissue specimens were evaluated to detect HPV DNA using ISH and PCR, and a concordance rate of 78.2% was found between these two modalities [32]. (LE: 3) A 63% histological and molecular agreement was observed in pap smear samples from lesions indicative of HPV infection [33].

6.4. Serology

Serology is used occasionally. When measured in cases of suspected HPV infection, 36% (18/50) of sera were positive for type-specific neutralizing antibodies. It is not used routinely, and use is limited to research settings [34]. (LE: 2b) It is important for studies on vaccine immunogenicity. In a cohort of 149 women (73 vaccinated), type-specific IgG seropositivity was very strongly associated with vaccination status. While, IgM seropositivity was observed with transient HPV infections [35].

In a population-based cohort (HELIUS study) including 532 women, vaginal HPV DNA detection by PCR was associated with type-specific HPV seropositivity (OR 1.53, 95% CI 1.06–2.20). Also, the geometric mean of type-specific antibody reactivity was 1.15 (95% CI 1.04–1.27) times higher in women positive for HPV DNA compared to HPV DNA-negative women [36].

Multiplex non-competitive Luminex-based immunoassay (ncLIA) is a validated, rapid, simple and inexpensive tool for measuring total IgG antibody response following natural infection or vaccination against four HPV types included in the quadrivalent vaccine. The correlation of serum antibody levels between the ncLIA and validation assay was highest for HPV16 and HPV11 ($r = 0.90$), followed by HPV6 ($r = 0.86$) and HPV18 ($r = 0.67$). The ncLIA was better able to predict HPV DNA positivity in genital samples than the validation assay for HPV16 (AUC 0.65 vs 0.52, $P = 0.001$) and HPV18 (AUC 0.71 vs 0.57, $P = 0.024$). AUCs for HPV6 and HPV11 were similar between the two assays (0.70 vs 0.71, $P = 0.59$, and 0.88 vs 0.96, $P = 0.08$, respectively) [37].

7. Prevention

It is important to educate individuals about the risk factors associated with HPV transmission and infection. Although there is no evidence that smoking cessation improves outcomes in patients with genital warts, it may be advised considering individual and public health. Condom use is only partially protective against HPV infection [38].

HPV DNA detected in the ablation smoke can cause lesions on the face and airways of medical staff performing ablative procedures like electrosurgery and CO_2 laser [39]. Usage of well-fitting N95 masks, smoke evacuators, and exhaust ventilation is necessary while performing smoke-generating procedures.

7.1. Vaccine

Cervarix and Gardasil are two prophylactic HPV vaccines designed primarily for cervical cancer prevention. Cervarix is effective against HPV16 and -18, the two most common cancer-causing types. Gardasil is also effective against HPV-16, 18, in addition, it is also effective against HPV-6 and -11, which are the most common types implicated in genital warts and respiratory papillomatosis. In 2014, a nine-valent vaccine, Gardasil 9 (Merck & Co., Kenilworth, NJ, USA), was licensed by the FDA, which offers protection against HPV-6, 11, 16, 18, 31, 33, 45, 53, and 58 [40]. Gardasil 9 can efficiently prevent infections and cervical cancer precursor lesions (>95%, injection prior to HPV exposure) of any grade

related to HPV types covered in the vaccine [40].

The Advisory Committee on Immunization Practices (ACIP) recommends HPV vaccination at age 11 or 12 years. Catch-up vaccination has been recommended for all persons through age 26 years. ACIP recommended shared clinical decision-making regarding potential HPV vaccination for persons aged 27–45 years as it may benefit some inadequately vaccinated persons who are at risk of new HPV infection [41].

The current generation of HPV vaccines, Cervarix and Gardasil have demonstrated a high degree of efficacy against HPV serotypes [42,43]. According to a systematic review and meta-analysis including data from vaccination programs of 14 high-income countries, after 5–8 years of HPV vaccination, anogenital wart diagnoses decreased significantly by 67% (relative risk [RR] 0·33, 95% CI 0·24-0·46) among girls aged 15–19 years, decreased significantly by 54% (RR 0·46, 95% CI 0.36–0.60) among women aged 20–24 years, and decreased significantly by 31% (RR 0·69, 95% CI 0·53-0·89) among women aged 25–29 years. Among boys aged 15–19 years anogenital wart diagnoses decreased significantly by 48% (RR 0·52, 95% CI 0·37-0·75) and among men aged 20–24 years they decreased significantly by 32% (RR 0·68, 95% CI 0·47-0·98) [42]. (LE:1a).

In a systematic review of studies from countries with high vaccine uptake like Australia and Denmark, HPV quadrivalent vaccine for women conferred herd protection with significant reduction in frequency of genital warts among unvaccinated young men [44]. (LE: 2a) However, the results from a meta-analysis suggests that HPV vaccination does not provide additional benefit with patients with previous anogenital warts and does not prevent their relapse [45]. (LE: 1a) The most important determinant of vaccine impact to reduce cervical cancer is its duration of efficacy. As per current evidence, the efficacy of Cervarix has been proven for 6.4 years and Gardasil's for 5 years [46]. Quadrivalent vaccine prevents infection with HPV-6, 11, 16, and 18 and the development of external genital lesions in males aged 16–26 years; the efficacy was 65.5% (95% CI, 45.8 to 78.6) for lesions related to HPV-6, 11, 16, or 18 [47].

7.2. Circumcision

Male circumcision has been reported to reduce HPV prevalence in men. However, there is no clear evidence. In a systematic review including 12149 circumcised and 12252 uncircumcised men, there was no significant association between circumcision and genital warts (OR 1.17; 95% CI 0.63–2.17), (LE: 2a) circumcision and genital HPV acquisition of new infections (OR 0.99; 95% CI 0.62–1.60), and genital HPV clearance (OR 1.38; 95% CI 0.96–1.97). In the same study, circumcision was found to significantly reduce the odds of genital HPV prevalence (OR 0.68; 95% CI 0.56–0.82), but there was substantial between-study heterogeneity ($I^2 = 70\%$) [48].

Conversely, a previous meta-analysis from Spain in which 21 studies with 8046 circumcised and 6336 uncircumcised men were included showed that male circumcision was associated with a statistically significant reduced genital HPV prevalence [49].

8. HIV and condyloma acuminata

Anogenital warts are much more frequent in human immunodeficiency (HIV)-positive patients compared to HIV-negative individuals. Anogenital warts of HIV-positive patients differ from those of HIV-negative individuals with respect to their spread, occurrence on more unusual anatomical sites, HPV-type spectrum, tendency to recur, and risk of malignant transformation. Eighteen to 56% of anogenital warts in HIV-positive patients harbour high-grade dysplasia [50]. The odds of developing anal carcinoma were 12.79 (95% CI 6.19–26.45; $P < 0.001$) times higher in individuals with a history of anogenital warts compared with individuals without a history of anogenital warts [51].

HIV-positive men have a high burden of genital HPV infection and anogenital warts. Men living with HIV with high CD4 count were more likely to clear anogenital warts than those with low CD4 count (adjusted hazard ratio 3.69; 95% CI 1.44–9.47) [52]. Anogenital warts of HIV-infected patients should be preferentially treated with ablative methods and suspicious lesions should be evaluated histopathologically.

9. Treatment

The preferred treatment modality based on the number and size of warts, and efficacy of the available therapies are summarized in Tables 1 and 2.

9.1. Provider administered

9.1.1. Photodynamic therapy

δ-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) is an effective technique in the treatment of condylomata acuminata. ALA-PDT is proposed to act by selective destruction of subclinical virus-shedding area and activation of specific immune cells in the lesional skin [53]. (LE: 1a) Significant differences were observed in HPV viral loads between pre-therapy and after one-three rounds of ALA-PDT treatment in patients with urethral condyloma acuminata. All patients (n=21) achieved complete clinical remission after the last session of ALA-PDT [54]. (LE:2C) The cervical condylomatous lesions have also shown good improvement with a low recurrence rate [55]. (LE: 3) After ALA-PDT, complete clearance of intra-anal rectal warts was seen in 76.1% (35 out of 46) patients and recurrence was observed in 5 patients after 12 weeks [56]. (LE:2C) Pain was observed in all patients with an average visual analog scale (VAS) pain score of 6.96 ± 1.41 points [56].

It has also been used in combination with CO2 laser, with decreased recurrence rate and increased clearance rate [57]. (LE: 1b) ALA-PDT has similar efficacy [98.42% (497/505) in ALA-PDT group vs 100% (195/195)] in CO_2 group; $p > 0.05$] but lower recurrence [10.77% (35/325) vs 33.33% (37/111); $p < 0.05$] rates compared to those of CO2 laser for the treatment of genital warts [58]. (LE:1B) In a systematic review of articles studying the different treatment modalities of urethral condylomas, ALA-PDT resulted in a higher rate of clearance on follow up (96%) compared to laser therapy (69%) and topical therapy (14%) ($p < 0.01$). But, adverse events were more frequent in the ALA-PDT group (69%) compared to laser therapy (28%) and topical treatment (30%) ($p < 0.01$) [59]. (LE:1A).

9.1.2. Laser

The CO_2, pulsed-dye, Argon, Holmium, and Nd:YAG lasers have been used in the treatment of anogenital warts. Single-period CO2 laser therapy was found to be beneficial for vulvar condylomata acuminata [60]. (LE: 3) The Nd:YAG and Thulium lasers have been used for external and urethral condylomas in 115 patients with complete clearance, however, 34% patients developed recurrences [61]. (LE: 2) Recurrent Buschke Löwenstein tumours were found to be treatable with CO2 laser vaporization with complete remission [62]. (LE: 3) [38] Diode

Table 1
Efficacy of various treatments for genital condyloma acuminata.

Treatment modality	Clearance rate (%)	Recurrence rate (%)
Photodynamic therapy	76–100	10–14
Laser	23–95	2.5–77
Surgery	89–93	18–65
Electrosurgery	35–94	20–25
Cryotherapy	46–96	18–39
Trichloroacetic acid	70–100	18–36
Immunotherapy	66–98	No recurrence after 3 months
Podophyllin	42–46.9	46–60
Imiquimod 5%	35–75	6
Podophyllotoxin	45–94	11–100
Sinecatechins	40–81	7–12
5-fluorouracil	10–50	50
Interferon	17–67	9–69

Table 2
Treatment summary.

Type of warts	Preferred treatment modality	Level of evidence
Few smaller lesions	Imiquimod 5% cream	1A, Gr A
	5-fluorouracil	1A, Gr A
	Polyphenon ointment	1A, Gr A
Few larger lesions	Surgery	1A, Gr A
	Cryotherapy	1B, Gr A
	Podophyllotoxin	1B, Gr A
Multiple lesions	Immunotherapy	1B, Gr A
	PDT	1B, Gr A
	Laser	2B, Gr B
	Combination therapies	1A, Gr B

laser coagulation resulted in a cure rate of 73% (33/45 patients) in small to large anogenital warts after a maximum of two sessions [63]. (LE:2b) In a retrospective study, Holmium laser had the highest clearance rate (92.2%) and lowest recurrence rate (14.3%) compared to cryotherapy, surgery and podophyllin ($p = 0.001$) in the treatment of genital warts [64]. (LE:3b) Single treatment with Holmium: YAG laser was effective in 57/60 patients (95%) with urethral warts. At a mean follow-up of 26 months, recurrences occurred in 8 patients (13.3%) [65]. (LE:2c) It is important to note that fumes from laser treatment contain contagious particles; masks and smoke evacuators should therefore be used.

In a retrospective study of 242 women treated with CO_2 laser in 2006–2007, the median time for recurrence was 14.6 weeks. Systematic follow-up for a median of 3.1 years revealed at least one recurrence in 68 (28.1%) of 242 women. Women with multifocal genital warts had a 2.9 times increased risk for recurrence compared to women with unifocal lesions ($p = 0.01$) [66]. (LE:2c) Holmium: YAG laser with ALA-PDT significantly reduced wart recurrence rates (17.6%) in comparison with CO2 laser with ALA-PDT (55%). Most warts (88.23%) were removed after a session of Holmium: YAG laser pretreatment. The average number of laser sessions required to clear all warts was 1.94 in the Holmium: YAG laser plus ALA-PDT group [67]. (LE:3b).

9.1.3. Surgery

Surgical excision is considered as the treatment of choice in large pedunculated lesions [68]. (LE: 3) Majority of patients can be treated under local anesthesia (1–2% lidocaine). Clearance rates of 89–93% have been reported for scissor excision, with recurrence rates of 18–65% [69]. Surgical excision is likely the most effective treatment for reducing risk of recurrence after complete clearance [70]. (LE:1a).

9.1.4. Electrosurgery

Electrosurgery uses high-frequency electrical currents to destroy anogenital warts and requires local anesthesia. Similar to lasers, fumes from electrosurgery contain contagious particles and hence preventative measures should be used. Clinical studies have shown clearance rates of 35–94% [69]. At one year after treatment, a cumulative recurrence rate of 8% (4/65, 95% CI 2–15%) was observed with electrosurgical excision of anal condylomas in HIV-infected men [71]. (LE:2c).

9.1.5. Cryotherapy

Cryotherapy acts by crystallizing the cytosol of the cells, resulting in cell necrosis and activation of immune system. It has a reported efficacy of 46–96% for wart clearance with recurrence in 18–39% of cases [69]. Weekly sessions are done usually up to 12 weeks for external genital warts [72]. (LE: 1b) It is an inexpensive, easy method with no serious side effects and is considered safe in pregnant women. Cryotherapy is safe and easy to apply in patients with externally accessible urethral condylomas. A mean number of 2.2 (1–5) sessions were required to eradicate clinically evident urethral condylomas without any complications like urethral obstruction [73]. Mild side effects as blistering, local necrosis, scarring and hypopigmentation can occur. Cryotherapy efficacy did not appear to differ from that of trichloroacetic acid, podophyllin, or imiquimod. Electrosurgery was weakly associated with better anogenital wart clearance than cryotherapy (RR 0.80, 95% CI 0.65–0.99) [74]. (LE:1a) Cryotherapy was associated with more immediate low-level adverse events (erythema, stinging, or irritation; RR 3.02, 95% CI 1.38–6.61) and immediate pain requiring oral analgesics (RR 2.11, 95% CI 1.07–4.17) but fewer erosions (RR 0.57, 95% CI 0.36–0.90) [74]. (LE:1a).

9.1.6. Trichloroacetic acid

Trichloroacetic acid (TCA) causes a chemical burn that destroys the anogenital warts. TCA is used in concentrations of 33–50% thrice weekly or 80–90% once weekly can be administered until the warts have cleared. It is most suitable for small acuminate or papular warts. Clinical studies have reported clearance rates of 70–100% [69]. Common side-effects include local discomfort, burning and ulceration. TCA can be used safely during pregnancy.

9.1.7. Immunotherapy

Intralesional antigen immunotherapy has been used for the treatment of warts. Induction of delayed type hypersensitivity is the proposed mechanism of action. L1-virus like particles (VLP) immunotherapy was found to be associated with a significantly reduced rate of recurrence of genital warts when used in combination with conventional destructive therapy [75]. (LE: 1b) In a randomized control trial of 89 patients, intralesional Mycobacterium w (Mw, the new nomenclature is Mycobacterium indicus pranii or MIP) vaccine showed similar efficacy and safety as of imiquimod 5% cream, with complete clearance in 66.7% of patients and a mean reduction in size of 83.23% [76]. (LE: 1b).

MMR vaccine is a safe and effective therapy for the treatment of anogenital warts. On average, a 42.4-percent response was observed in the first three weeks after administering the MMR vaccine, which increased to 75.8% after the second vaccine at six weeks and nearly 98% after the last vaccine at nine weeks [77]. (LE: 2c).

9.1.8. Podophyllin

Topical solution of 20% podophyllin is applied by physician, once a week for up to eight weeks. It is an antimitotic and antiproliferative agent. Local side effects in the form of edema, inflammation and erosions can be seen [78]. (LE: 1b) It is contraindicated during pregnancy. However, a recent analysis of a cohort of 9229 pregnancies from January 1997 to December 2016 suggested that podophyllotoxin did not appear to be associated with an increased risk of adverse fetal outcomes during pregnancy and may be safe for use during pregnancy [79]. (LE:2b).

A combination of one or two sessions of cryo-destruction with 25% podophyllin as the cytotoxic agent, and post-ablation immunomodulation with topical sinecatechins 15% ointment resulted in an initial clearance rate of 96.3% with a recurrence rate of 7.4% after a total period of six months of follow-up in 27 patients with external genital warts [80]. (LE: 2c).

9.2. Patient administered

9.2.1. Imiquimod 5%

Imiquimod 5% cream is a topical immune response modifier, which has antiviral and anti-tumor properties by inducing the production of cytokines (interleukins, interferons, TNF-alpha). Imiquimod is recommended for anogenital warts as topical application three times every week till complete clearance of wart or maximum 16 weeks [81]. (LE: 1b) In terms of complete clearance, imiquimod 5% cream had significantly better therapeutic efficacy compared with imiquimod 1% (OR 0.21, 95% CI 0.14–0.34), 2.5% (OR 0.25, 95% CI 0.13–0.49) and 3.75% (OR 0.36, 95% CI 0.18–0.70) creams [82]. (LE: 1a) Imiquimod 3.75% cream, which is approved in USA and Canada, appears to be as effective as 5% when applied daily for 8 weeks and is said to increase tolerability,

decrease treatment duration and side effects. (LE: 3) [44].

Imiquimod 5% cream can cause severe erythema and erosions leading to treatment discontinuation in 40% of patients [82]. It should not be used for warts involving the urethral orifice, cervix, anus, and rectum. In a recent study, imiquimod 5% cream applied to intra-anal warts was found to be as efficacious (complete clearance rate of 36.8% (7/19) at week 16, 70% (7/10) at week 28) as when applied to external anogenital warts but adverse events were observed in 81% (17/21) of patients with intra-anal warts [83]. (LE:2c) A retrospective study of 60 patients with anogenital warts showed that the recurrence rate during long-term follow-up (up to 7 years) was lower for patients with complete responses to imiquimod 5% monotherapy (15%), or with surgical removal of residual warts after imiquimod 5% (20%), compared with surgery alone (65%) [84]. (LE:2C).

9.2.2. Podophyllotoxin

Podophyllotoxin inhibits the proliferation of human skin keratinocytes and cures genital warts by inhibiting proliferation of HPV-infected cells. Podophyllotoxin is used twice daily on 3 consecutive days every week until warts are completely cleared, or for a maximum period of 4 weeks. Clearance rates from clinical studies range from 45 to 94%, with common side-effects including pain, itching, burning, erosion and inflammation [69]. In a randomized controlled trial comparing the effectiveness of self-applied podophyllotoxin 0.5% solution and podophyllotoxin 0.15% cream, compared to clinic applied 25% podophyllin in treating anogenital warts, complete clearance was seen in 75%, 64.5% and 53.1% of patients respectively [85]. (LE: 1b).

The combination of podophyllotoxin and cryotherapy showed a significantly higher efficacy in the treatment of genital warts in men compared to monotherapy with podophyllotoxin after 6 weeks of treatment ($P < 0.001$), with considerably lower recurrence and appearance of new warts compared with cryotherapy during the 6-month periodafter therapy ($P < 0.005$) [86]. (LE:1b) In a systematic review and network meta-analysis, podophyllotoxin 0.5% solution was found to be significantly more effective than imiquimod 5% cream (OR 0.07, 95% credible interval [CrI] 0.001 to 0.36) at achieving complete clearance at the end of treatment [70]. (LE: 1a) In addition, podophyllotoxin was found to be more effective than imiquimod for anogenital warts on keratinized sites. In patients with lesions on dry, keratinized anatomical sites, the complete clearance rates were 7.6% for imiquimod and 27.9% for podophyllotoxin ($P < 0.001$) and no difference was noted with lesions on moist, partially keratinized sites [87]. (LE:2b).

9.2.3. Sinecatechins and polyphenon E 10% ointment

Sinecatechins are derived from green tea leaves of the Camellia sinensis species containing the active ingredient epigallocatechingallate (EGCG; Polyphenon E). Anti-viral, immune stimulation and anti-carcinogenic activity are the proposed mechanism of actions. It is formulated as a 10% ointment while a 15% preparation is only available in the US. There are no significant differences in response rates between the two formulations [88]. (LE:1a) Three times daily application is recommended till complete wart clearance or maximum 16 weeks. Polyphenon E 10% ointment is generally well tolerated in adults with external genital and perianal warts. Mild local side effects can be noted as redness, burning, pain, itching and swelling [89]. (LE: 3) Sinecatechins have resulted in complete clearance rates of 40–81% with around 7–11% recurrence rate [69,90]. (LE:1a) In a prospective multicenter trial, the use of sinecatechins 10% as proactive sequential therapy after ablative treatment with CO2 laser was associated with a lower recurrence rate of new external genital warts in the short term in comparison with CO2 laser alone (Recurrence rate: 5% vs. 29%, $p = 0.0024$; OR 0.16; 95% CI 0.04–0.68) [91]. (LE:1b).

9.2.4. Cidofovir

Cidofovir is a nucleotide analog of deoxycytidine monophosphate. It selectively competitively inhibits viral DNA polymerase. Topical cidofovir has been successfully used in the management of condyloma acuminatum and other HPV-mediated diseases, especially in the immunocompromised and in patients with recalcitrant warts [92]. (LE: 3).

9.2.5. 5-Fluorouracil (5-FU)

5-Fluorouracil is a pyrimidine anti-metabolite that functions as an anti-neoplastic agent by blocking DNA synthesis. Daily application of 5% 5-FU cream has been found to be effective in external genital and perianal warts [93]. (LE: 1a) A randomized controlled trial including 72 patients demonstrated that there was no significant difference in the efficacy between 1% 5-FU cream and 90% TCA ($p = 0.763$) or between 5% 5-FU cream and 90% TCA ($p = 0.274$) after 7 weeks of treatment. Subjective side-effects with 1% and 5% 5-FU were significantly milder than 90% TCA [94]. (LE:1b).

9.2.6. Interferon

It acts in HPV infections by virtue of its antiviral, anti-proliferative mechanisms. In addition, it also stimulates the immune system of the body. It can be used either by intralesional route or systemic routes (subcutaneous or intramuscular), the former being more effective [95]. (LE: 1a) Biphasic vesicles for topical delivery of interferon alpha are also available [96]. Studies investigating the efficacy of adjuvant systemic interferon after ablative treatment have yielded inconsistent results. Compared with placebo, adjuvant alpha-, beta- and gamma-interferon were neither significantly superior in terms of complete clearance over the short, intermediate or long term, nor with regard to intermediate- or long-term recurrence [97]. (LE:1a).

Other treatment modalities like low-dose oral cyclophosphamide therapy [98] (LE: 4), systemic interleukin 2 and topical cidofovir [92] (LE: 4), local hyperthermia 44°c [99] (LE: 4), oral retinoid and intramuscular interferon-γ therapy [100] (LE: 4), combination of radiofrequency surgical dissection and oral acitretin [101] (LE: 3), a radionuclide 32P application device for the treatment of condyloma acuminatum in the rectum [102] (LE: 1b), adjuvant oral pidotimod plus vitamin C after laser vaporization [103] (LE: 1b), chemoradiotherapy for large Buschke-Lowenstein tumor [104] (LE: 3), topical nitric-zinc complex [105] (LE:2c), and topical sodium nitrate with citric acid [106] (LE:1b) have been tried.

Declaration of competing interest

None.

Acknowledgement

None.

References

[1] Hirth J. Disparities in HPV vaccination rates and HPV prevalence in the United States: a review of the literature. Hum Vaccines Immunother 2019;15(1):146–55.
[2] Hathaway JK. HPV: diagnosis, prevention, and treatment. Clin Obstet Gynecol 2012;55(3):671–80.
[3] Park YJ, Kim JM, Lee BR, Kim TH, Lee EG. Annual prevalence and economic burden of genital warts in Korea: health Insurance Review and Assessment (HIRA) service data from 2007 to 2015. Epidemiol Infect 2018;146(2):177–86.
[4] Flagg EW, Torrone EA. Declines in anogenital warts among age groups most likely to Be impacted by human papillomavirus vaccination, United States, 2006-2014. Am J Publ Health 2018;108(1):112–9.
[5] Yakely AE, Niccolai LM, Oliveira CR. Trends in anogenital wart diagnoses in Connecticut, 2013-2017. JAMA Netw Open 2020;3(1):e1920168.
[6] Kawado M, Hashimoto S, Ohta A, Oba MS, Uehara R, Taniguchi K, et al. Estimating nationwide cases of sexually transmitted diseases in 2015 from sentinel surveillance data in Japan. BMC Infect Dis 2020;20(1):77.
[7] Khopkar US, Rajagopalan M, Chauhan AR, Kothari-Talwar S, Singhal PK, Yee K, et al. Prevalence and burden related to genital warts in India. Viral Immunol 2018;31(5):346–51.

[8] Tsai T-F, Kothari-Talwar S, Yee K, Kulkarni A, Lara N, Roset M, et al. Estimating the burden of genital warts in Taiwan. Sex Health 2017;14(6):485–91.
[9] Lee TS, Kothari-Talwar S, Singhal PK, Yee K, Kulkarni A, Lara N, et al. A cross-sectional study estimating the burden of illness related to genital warts in South Korea. BMJ Open 2017;7(6):e014217.
[10] Zhu C, Wang Y, Mao W, Zhang H, Ma J. Prevalence and distribution of HPV types in genital warts in Xi'an, China: a prospective study. BMJ Open 2019;9(5):e023897.
[11] Nilyanimit P, Chansaenroj J, Srisomboon J, Rodrangnok W, Rajakom N, Daengsaard E, et al. Human papillomavirus in Thai women and men with anogenital warts. Intervirology 2018;61(5):223–9.
[12] Lin C-C, Hsieh M-C, Hung H-C, Tsao S-M, Chen S-C, Yang H-J, et al. Human papillomavirus prevalence and behavioral risk factors among HIV-infected and HIV-uninfected men who have sex with men in Taiwan. Medicine (Baltim) 2018;97(45):e13201.
[13] Zhou Y, Lin Y-F, Gao L, Dai J, Luo G, Li L, et al. Human papillomavirus prevalence among men who have sex with men in China: a systematic review and meta-analysis. Eur J Clin Microbiol Infect Dis 2021;40(7):1357–67.
[14] Suzuki S, Sekizawa A, Tanaka M, Matsuda H, Okai T, Kinoshita K, et al. Current status of condylomata acuminata in pregnant Japanese women. Jpn J Infect Dis 2016;69(4):347–9.
[15] Hansen BT, Hagerup-Jenssen M, Kjaer SK, Munk C, Tryggvadottir L, Sparén P, et al. Association between smoking and genital warts: longitudinal analysis. Sex Transm Infect 2010;86(4):258–62.
[16] Petca A, Borislavschi A, Zvanca ME, Petca R-C, Sandru F, Dumitrascu MC. Non-sexual HPV transmission and role of vaccination for a better future (Review). Exp Ther Med 2020;20(6):186.
[17] Lauro C, Ammaturo FP, Quirino L, Rotondi M, Soriano A, Panariello S. [Evaluation of partners of women with HPV infection]. Minerva Ginecol 2000;52(12):503–7.
[18] Giuliano AR, Lee J-H, Fulp W, Villa LL, Lazcano E, Papenfuss MR, et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. Lancet 2011;377(9769):932–40.
[19] Giuliano AR, Anic G, Nyitray AG. Epidemiology and pathology of HPV disease in males. Gynecol Oncol 2010;117(2 Suppl):S15–9.
[20] Rymark P, Forslund O, Hansson BG, Lindholm K. Genital HPV infection not a local but a regional infection: experience from a female teenage group. Genitourin Med 1993;69(1):18–22.
[21] Lynde C, Vender R, Bourcier M, Bhatia N. Clinical features of external genital warts. J Cutan Med Surg 2013;17(Suppl 2):S55–60.
[22] McCutcheon T. Anal condyloma acuminatum. Gastroenterol Nurs 2009;32(5):342–9.
[23] Delbello A, Colli C, Martínez T del R, Trevisan G. Anal canal and rectal condylomatosis: exhaustive proctological examination and STD patients. Acta Dermatovenerol Alpina Pannonica Adriatica 2010;19(1):13–6.
[24] Cong X, Sun R, Zhang X, Wang Y, Wang L, Yu Y. Correlation of human papillomavirus types with clinical features of patients with condyloma acuminatum in China. Int J Dermatol 2016;55(7):775–80.
[25] Wieland U, Kreuter A, Pfister H. Human papillomavirus and immunosuppression. Curr Probl Dermatol 2014;45:154–65.
[26] Strand A, Rylander E. Human papillomavirus. Subclinical and atypical manifestations. Dermatol Clin 1998;16(4):817–22.
[27] Kazlouskaya V, Shustef E, Allam SH, Lal K, Elston D. Expression of p16 protein in lesional and perilesional condyloma acuminata and bowenoid papulosis: clinical significance and diagnostic implications. J Am Acad Dermatol 2013;69(3):444–9.
[28] Kalof AN, Cooper K. p16INK4a immunoexpression: surrogate marker of high-risk HPV and high-grade cervical intraepithelial neoplasia. Adv Anat Pathol 2006;13(4):190–4.
[29] Gardner KM, Crawford RI. Distinction of condylomata acuminata from vulvar vestibular papules or pearly penile papules using Ki-67 immunostaining. J Cutan Med Surg 2019;23(3):255–7.
[30] Mills A, Balasubramaniam R, Longacre TA, Kong CS, Pinsky BA. Laboratory-developed L1 sequencing and type-specific, real-time polymerase chain reaction for the detection and typing of human papillomaviruses in formalin-fixed, paraffin-embedded tissues. Arch Pathol Lab Med 2013;137(1):50–4.
[31] Fernández-Nestosa MJ, Guimerà N, Sanchez DF, Cañete-Portillo S, Velazquez EF, Jenkins D, et al. Human papillomavirus (HPV) genotypes in condylomas, intraepithelial neoplasia, and invasive carcinoma of the penis using laser capture microdissection (LCM)-PCR: a study of 191 lesions in 43 patients. Am J Surg Pathol 2017;41(6):820–32.
[32] Kelesidis T, Aish L, Steller MA, Aish IS, Shen J, Foukas P, et al. Human papillomavirus (HPV) detection using in situ hybridization in histologic samples: correlations with cytologic changes and polymerase chain reaction HPV detection. Am J Clin Pathol 2011;136(1):119–27.
[33] Laabidi B, Ben Rejeb S, Bani A, Mansouri N, Lamine O, Bouzaini A, et al. Human papillomavirus detection using in situ hybridization and correlations with histological and cytological findings. Med Maladies Infect 2016;46(7):380–4.
[34] Wu X, Zhang C, Zhu X, Wang Y. Detection of HPV types and neutralizing antibodies in women with genital warts in Tianjin City, China. Virol Sin 2010;25(1):8–17.
[35] Murall CL, Reyné B, Selinger C, Bernat C, Boué V, Grasset S, et al. HPV cervical infections and serological status in vaccinated and unvaccinated women. Vaccine 2020;38(51):8167–74.
[36] Kovaleva A, Alberts CJ, Waterboer T, Michel A, Snijder MB, Vermeulen W, et al. A cross-sectional study on the concordance between vaginal HPV DNA detection and type-specific antibodies in a multi-ethnic cohort of women from Amsterdam, The Netherlands - the HELIUS study. BMC Infect Dis 2016;16(1):502.
[37] Trevisan A, Wissing MD, Dagenais C, Forest P, Ramanakumar AV, Burchell AN, et al. Development and evaluation of a new non-competitive Luminex immunoassay detecting antibodies against human papillomavirus types 6, 11, 16 and 18. J Gen Virol 2021;102(5).
[38] Juckett G, Hartman-Adams H. Human papillomavirus: clinical manifestations and prevention. Am Fam Physician 2010;82(10):1209–13.
[39] Palma S, Gnambs T, Crevenna R, Jordakieva G. Airborne human papillomavirus (HPV) transmission risk during ablation procedures: a systematic review and meta-analysis. Environ Res 2021;192:110437.
[40] Cheng L, Wang Y, Du J. Human papillomavirus vaccines: an updated review. Vaccines (Basel) 2020;8(3):391.
[41] Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the advisory committee on immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68(32):698–702.
[42] Drolet M, Bénard É, Pérez N, Brisson M, HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet 2019;394(10197):497–509.
[43] Lukács A, Máté Z, Farkas N, Mikó A, Tenk J, Hegyi P, et al. The quadrivalent HPV vaccine is protective against genital warts: a meta-analysis. BMC Publ Health 2020;20(1):691.
[44] Garland SM, Kjaer SK, Muñoz N, Block SL, Brown DR, DiNubile MJ, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 Years of real-world experience. Clin Infect Dis 2016;63(4):519–27.
[45] H Husein-ElAhmed. Could the human papillomavirus vaccine prevent recurrence of ano-genital warts?: a systematic review and meta-analysis. Int J STD AIDS 2020;31(7):606–12.
[46] Harper DM. Currently approved prophylactic HPV vaccines. Expert Rev Vaccines 2009;8(12):1663–79.
[47] Giuliano AR, Palefsky JM, Goldstone S, Moreira ED, Penny ME, Aranda C, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med 2011;364(5):401–11.
[48] Zhu Y-P, Jia Z-W, Dai B, Ye D-W, Kong Y-Y, Chang K, et al. Relationship between circumcision and human papillomavirus infection: a systematic review and meta-analysis. Asian J Androl 2017;19(1):125–31.
[49] Albero G, Castellsagué X, Giuliano AR, Bosch FX. Male circumcision and genital human papillomavirus: a systematic review and meta-analysis. Sex Transm Dis 2012;39(2):104–13.
[50] Wieland U, Kreuter A. [Genital warts in HIV-infected individuals]. Hautarzt 2017;68(3):192–8.
[51] Arnold JD, Byrne ME, Monroe AK, Abbott SE. District of Columbia cohort executive committee. The risk of anal carcinoma after anogenital warts in adults living with HIV. JAMA Dermatol 2021;157(3):283–9.
[52] Chikandiwa A, Pisa PT, Muller EE, Tamalet C, Mayaud P, Chersich MF, et al. Incidence, persistence, clearance, and correlates of genital human papillomavirus infection and anogenital warts in a cohort of men living with human immunodeficiency virus in South Africa. Sex Transm Dis 2019;46(5):347–53.
[53] Ying Z, Li X, Dang H. 5-aminolevulinic acid-based photodynamic therapy for the treatment of condylomata acuminata in Chinese patients: a meta-analysis. Photodermatol Photoimmunol Photomed 2013;29(3):149–59.
[54] Xie J, Ao C, Li J, Jiang L, Liu H, Zeng K. 5-aminolevulinic acid photodynamic therapy for condyloma acuminatum of urethral meatus. J Dermatol Treat 2019;30(7):714–7.
[55] Chen M-K, Luo D-Q, Zhou H, Huang Z-W, Zhang Q-F, Han J-D. 5-aminolevulinic acid-mediated photodynamic therapy on cervical condylomata acuminata. Photomed Laser Surg 2011;29(5):339–43.
[56] Zhao W, Shan X-F, Wang C-L, Liu X-Z, Li Z, Xiao H-L, et al. Topical 5-aminolevulinic acid photodynamic therapy for intra anal-rectal warts. J Dermatol Treat 2020;31(3):241–4.
[57] Hu S, Yang Y, Jiang B, Su D, Zhang L, Huang Z, et al. Treatment of condyloma acuminatum using the combination of laser ablation and ALA-PDT. Photodiagnosis Photodyn Ther 2019;25:193–6.
[58] Tu P, Zhang H, Zheng H, Gu H, Xu J, Tao J, et al. 5-Aminolevulinic photodynamic therapy versus carbon dioxide laser therapy for small genital warts: a multicenter, randomized, open-label trial. J Am Acad Dermatol 2021;84(3):779–81.
[59] Kechichian E, Helou E, Sarkis J, Hayek C, Labaki C, Nemr E, et al. The place of 5-aminolaevulinic acid-photodynamic therapy in the treatment landscape of urethral warts: a systematic review. Photodiagnosis Photodyn Ther 2021;33:102204.
[60] Li X, Zhu L, Gu Y, Jin H, Wang C, Xu T, et al. [Outcome prediction of single-period CO(2) laser therapy for vulvar condylomata acuminate]. Zhonghua Yixue Zazhi 2012;92(25):1759–62.
[61] Blokker RS, Lock TMTW, de Boorder T. Comparing thulium laser and Nd:YAG laser in the treatment of genital and urethral condylomata acuminata in male patients. Laser Surg Med 2013;45(9):582–8.
[62] Perniola G, d'Itri F, Di Donato V, Achilli C, Lo Prete E, Panici PB. Recurrent Buschke-Löwenstein tumor treated using CO(2) laser vaporization. J Minim Invasive Gynecol 2010;17(5):662–4.
[63] Alharbi R, Clanner-Engelshofen B, Hildebrand JA, Schinabeck-Kühne N, Niculescu L, French LE, et al. Diode lasers for the treatment of genital warts. Eur J Dermatol 2019;29(4):409–16.

[64] Ghiasy S, Fallah-Karkan M, Razzaghi MR, Ranjbar A, Rahavian A, Javanmard B. Is holmium laser an appropriate modality to treat genital warts? J Laser Med Sci 2019;10(1):70–4.
[65] Del Zingaro M, Cochetti G, Zucchi A, Paladini A, Rossi De Vermandois JA, Ciarletti S, et al. Holmium:YAG laser for the treatment of genital and urethral warts: multicentre prospective evaluation of safety and efficacy. J Laser Med Sci 2021;12:e34.
[66] Widschwendter A, Böttcher B, Riedl D, Coban S, Mutz-Dehbalaie I, Matteucci Gothe R, et al. Recurrence of genitals warts in pre-HPV vaccine era after laser treatment. Arch Gynecol Obstet 2019;300(3):661–8.
[67] Liao C, Sun X, Zhang G, Zhang H, Zhang L, Wang X. Advanced application of holmium: YAG laser combined ALA-PDT for the treatment of refractory condylomata acuminata in anal canal. Photodiagnosis Photodyn Ther 2020;30:101696.
[68] Qian G, Yu H. Giant condyloma acuminata of Buschke-Lowenstein: successful treatment mainly by an innovative surgical method. Dermatol Ther 2013;26(5):411–4.
[69] O'Mahony C, Gomberg M, Skerlev M, Alraddadi A, de las Heras-Alonso ME, Majewski S, et al. Position statement for the diagnosis and management of anogenital warts. J Eur Acad Dermatol Venereol 2019;33(6):1006–19.
[70] Barton S, Wakefield V, O'Mahony C, Edwards S. Effectiveness of topical and ablative therapies in treatment of anogenital warts: a systematic review and network meta-analysis. BMJ Open 2019;9(10):e027765.
[71] Vela S, Videla S, Ornelas A, Revollo B, Clotet B, Sirera G, et al. Effectiveness of physically ablative and pharmacological treatments for anal condyloma in HIV-infected men. PLoS One 2018;13(8):e0199033.
[72] Gilson RJC, Ross J, Maw R, Rowen D, Sonnex C, Lacey CJN. A multicentre, randomised, double-blind, placebo controlled study of cryotherapy versus cryotherapy and podophyllotoxin cream as treatment for external anogenital warts. Sex Transm Infect 2009;85(7):514–9.
[73] Vives Á, 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.
[74] 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.
[75] Jardine D, Lu J, Pang J, Palmer C, Tu Q, Chuah J, et al. A randomized trial of immunotherapy for persistent genital warts. Hum Vaccin Immunother 2012;8(5):623–9.
[76] Kumar P, Dar L, Saldiwal S, Varma S, Datt Upadhyay A, Talwar D, et al. Intralesional injection of Mycobacterium w vaccine vs imiquimod, 5%, cream in patients with anogenital warts: a randomized clinical trial. JAMA Dermatol 2014;150(10):1072–8.
[77] Sharma S, Agarwal S. Intralesional immunotherapy with Measles Mumps Rubella vaccine for the treatment of anogenital warts: an open-label study. J Clin Aesthet Dermatol 2020;13(8):40–4.
[78] Akhavan S, Mohammadi SR, Modarres Gillani M, Mousavi AS, Shirazi M. Efficacy of combination therapy of oral zinc sulfate with imiquimod, podophyllin or cryotherapy in the treatment of vulvar warts. J Obstet Gynaecol Res 2014;40(10):2110–3.
[79] Andersson NW, Andersen JT. Association between fetal safety outcomes and exposure to local podophyllotoxin during pregnancy. JAMA Dermatol 2020;156(3):303–11.
[80] Juhl ME, Seferovic V, Antonijevic S, Krunic A. Combined treatment of anogenital HPV infection with cryodestruction, podophyllin 25% and post-ablation immunomodulation with sinecatechins 15% ointment - a retrospective analysis. Int J STD AIDS 2016;27(12):1071–8.
[81] 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.
[82] Jung JM, Jung CJ, Lee WJ, Won CH, Lee MW, Choi JH, et al. Topically applied treatments for external genital warts in nonimmunocompromised patients: a systematic review and network meta-analysis. Br J Dermatol 2020;183(1):24–36.
[83] Irisawa R, Tsuboi R, Saito M, Harada K. Treatment of intra-anal warts with imiquimod 5% cream: a single-center prospective open study. J Dermatol 2021;48(4):476–80.
[84] 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.
[85] Lacey CJN, 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.
[86] Golušin Z, Jovanović M, Matić M, Roš T, Vujanović L, Nikolić O. Clinical efficacy of combination therapy with podophyllotoxin and liquid nitrogen cryotherapy in the treatment of genital warts in men. Acta Dermatovenerol Croat 2019;27(4):250–9.
[87] Nicolaidou E, Kanelleas A, Nikolakopoulos S, Bezrodnii G, Nearchou E, Gerodimou M, et al. A short, 8-week course of imiquimod 5% cream versus podophyllotoxin in the treatment of anogenital warts: a retrospective comparative cohort study. Indian J Dermatol Venereol Leprol 2021;87(5):666–70.
[88] Werner RN, Westfechtel L, Dressler C, Nast A. Self-administered interventions for anogenital warts in immunocompetent patients: a systematic review and meta-analysis. Sex Transm Infect 2017;93(3):155–61.
[89] Fantasia HC. Sinecatechins ointment 15% for the treatment of external genital warts. Nurs Womens Health 2012;16(5):418–22.
[90] Gilson R, Nugent D, Werner RN, Ballesteros J, Ross J. IUSTI-Europe guideline for the management of anogenital warts. J Eur Acad Dermatol Venereol 2019;34(8):1644–53. 2020.
[91] Puviani M, Galluzzo M, Talamonti M, Mazzilli S, Campione E, Bianchi L, et al. Efficacy of sinecatechins 10% as proactive sequential therapy of external genital warts after laser CO2 ablative therapy: the PACT study (post-ablation immunomodulator treatment of condylomata with sinecatechins): a randomized, masked outcome assessment, multicenter trial. Int J STD AIDS 2019;30(2):131–6.
[92] Nambudiri VE, Mutyambizi K, Walls AC, Fisher DC, Bleday R, Saavedra AP. Successful treatment of perianal giant condyloma acuminatum in an immunocompromised host with systemic interleukin 2 and topical cidofovir. JAMA Dermatol 2013;149(9):1068–70.
[93] 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.
[94] Anggraini I, Hoemardani AS, Nilasari H, Indriatmi W. Randomised controlled trial of 1% and 5% 5-fluorouracil creams compared with 90% trichloroacetic acid solution for anogenital wart treatment. Int J STD AIDS 2020;31(9):849–58.
[95] Yang J, Pu YG, Zeng ZM, Yu ZJ, Huang N, Deng QW. Interferon for the treatment of genital warts: a systematic review. BMC Infect Dis 2009;9:156.
[96] Foldvari M, Badea I, Kumar P, Wettig S, Batta R, King MJ, et al. Biphasic vesicles for topical delivery of interferon alpha in human volunteers and treatment of patients with human papillomavirus infections. Curr Drug Deliv 2011;8(3):307–19.
[97] Westfechtel L, Werner RN, Dressler C, Gaskins M, Nast A. Adjuvant treatment of anogenital warts with systemic interferon: a systematic review and meta-analysis. Sex Transm Infect 2018;94(1):21–9.
[98] Zhang Y, Duan Y, Zhao J, Huang B, Cao Y. Low-dose oral cyclophosphamide therapy is effective for condylomata acuminata. Chin Med J (Engl) 2013;126(16):3198–9.
[99] Huo W, Li G-H, Qi R-Q, Zhang L, Yan X-X, Chen H-D, et al. Clinical and immunologic results of local hyperthermia at 44 °C for extensive genital warts in patients with diabetes mellitus. Int J Hyperther 2013;29(1):17–20.
[100] Tian YP, Yao L, Malla P, Song Y, Li SS. Successful treatment of giant condyloma acuminatum with combination retinoid and interferon-γ therapy. Int J STD AIDS 2012;23(6):445–7.
[101] Mavrogianni P, Fallidas E, Nicolaidou E, Villias K, Stefanaki I, Katsambas A, et al. Therapeutic combination of radiofrequency surgical dissection and oral acitretin in the management of perianal Buschke-Lowenstein tumour: a case report. Int J STD AIDS 2012;23(5):362–4.
[102] Ma Y, Liu Y, Gu A, Xu F, Liu P, Yuan S, et al. [A 32P application device for the treatment of condyloma acuminatum in the rectum]. Zhonghua Nan ke Xue 2011;17(1):47–51.
[103] Zervoudis S, Iatrakis G, Peitsidis P, Peitsidou A, Papandonopolos L, Nikolopoulou MK, et al. Complementary treatment with oral pidotimod plus vitamin C after laser vaporization for female genital warts: a prospective study. J Med Life 2010;3(3):286–8.
[104] Armstrong N, Foley G, Wilson J, Finan P, Sebag-Montefiore D. Successful treatment of a large Buschke-Lowenstein tumour with chemo-radiotherapy. Int J STD AIDS 2009;20(10):732–4.
[105] 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 2019;9(2):327–35.
[106] Ormerod AD, van Voorst Vader PC, Majewski S, Vanscheidt W, Benjamin N, van der Meijden W. Evaluation of the efficacy, safety, and tolerability of 3 dose regimens of topical sodium nitrite with citric acid in patients with anogenital warts: a randomized clinical trial. JAMA Dermatol 2015;151(8):854–61.