

# Genital warts: New approaches to the treatment

Zoran GOLUŠIN\*

Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad

\*Correspondence: Dr Zoran Golušin, E-mail: zgolusin@eunet.yu

UDC 616.97:[616.988:578.827.12



## Abstract

Genital warts are one of the most common sexually transmitted infections caused by the human papilloma virus. Persons with genital warts may be infected by several types of human papilloma viruses: various types may have antagonistic or synergistic interactions, causing regression or recurrence of the existing lesions. No specific antiviral therapy is currently available. The treatment includes removal of symptomatic lesions on the skin and mucous surfaces. Apart from classical surgical procedures, local destruction of lesions is performed using various chemical and physical agents, whereas systemic therapy includes administration of agents promoting the immune system. The efficacy of treatment is not identical in all cases, and relapses are still inevitable. Combination therapy is often an alternative to monotherapy, while vaccine has an important role in prevention of genital warts.

Genital warts (GWs) (lat. *Condylomata acuminata*) are visual manifestations of genital human papilloma virus (HPV) infection, and they are among the most common sexually transmitted diseases (STDs) in developed countries. Due to their high prevalence, viral etiopathogenesis and still inefficient therapy, GWs represent a complex clinical problem in dermatology and venereology.

## Epidemiology

Genital warts are a clinical manifestation of HPV infection in 1% of the sexually active population. The incidence of GWs is around 2,4 per 1000 inhabitants of Western Europe, and 8 per 1000 females in North America. The incidence is ten times higher among HIV (eng. Human Immunodeficiency Virus) positive individuals (1, 2). Genital warts are the most common viral sexually transmitted infection in the Great Britain (3). The highest prevalence of GWs is established among people from 20 – 24 years of age, and it is around 0.6 to 1.2% in both sexes (1, 4). In 2000, it was estimated that in the US, 6.2 million people, aged 15 – 44 years, are infected with GWs (5). The infection affects men and women equally, but it is also seen in the pediatric population. Vertical transmission and sexual transmission are the main routes of acquisition at an early age (6).

## Etiology and immunology

The viral etiology of GWs was recognized in 1907 (7), whereas HPV was identified as the virus responsible for GWs in the mid-seventies of the last century (8). This group of viruses of epithelial epidermotropic nature may invade various parts of the body, including the skin, mucosal surfaces of the mouth, larynx, esophagus, and of the anogenital tract. More than 120 types of HPV have been identified, and approximately 30 of them have been associated with genital epithelial infection (HPV-type 6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 52, 53, 55, 56, 57, 58, 59, 68...) (9). HPV-16 and HPV-18 are the most commonly detected types in men (10).

The cellular immune system plays a major role in the regression of HPV-induced genital diseases. Spontaneous regression of GWs is associated with significant increase in CD4+ T-lymphocytes in the dermis and epidermis. Anti-HPV antibodies are detected in the sera of patients with GWs (9). Immunosuppression is considered a condition *sine qua non*, especially in HIV-positive patients, who are 10 times more susceptible to genital warts (1, 2). However, the highest incidence of genital warts is observed among adolescents (1, 4). In the United States, it has been established that 3 million cases of sexually transmitted infections (STI) occur in

adolescents each year and that every fourth sexually active adolescent gets a STI before the age of 18 (11). Taking into consideration the threatening results of the research performed among high-risk teenagers in the United States, revealing a significant immune deficiency even in HIV-negative persons, it is obvious that immune deficiency is directly associated with high prevalence of STI in this age group (12).

Patients with GWs may be infected with various types of HPV at the same time (13). It has been established that during infection different types of viruses may have antagonistic or synergistic effects on other types of HPV, which can be an explanation for frequent spontaneous regression and recurrence of skin and mucous lesions (14). Spontaneous regression of GWs occurs in up to 30% of affected patients during a 4-month period (9).

### Risk factors

Studies have shown that the association between HPV genital infection and promiscuity significantly increases the risk of GWs in women in regard to men. Other risk factors include lack of condom use and immunosuppression (15). HPV is transmitted by direct skin-to-skin and mucous membrane contact. Cervical infection may be caused by HPV transmitted from the external genitalia (16). Transmission of HPV through routes other than sexual is also possible, and it must not be forgotten. HPV was detected on the fingers of persons with GWs (17). Transmission is possible by using sexual aids as well. Moreover, HPV infection was found in 6.1% of women who have never had sexual intercourse (18). The incubation period of genital HPV infections is rather long, from 2 to 9 months, although there are data about the possible range of incubation from 6 weeks to several years (21). Most infected individuals remain asymptomatic; on average, the infection lasts from several months to 2 years, while the final stage of infection is also asymptomatic. The virus is detected only by HPV DNA testing (19, 20).

There is strong evidence for an association between HPV infection and anogenital cancers. HPV can be identified in 93% of invasive cervical cancers, primarily HPV type 16 (21). HPV is also diagnosed in 42% of patients with penile carcinomas; while HPV type 16 is also most frequent (22, 23, 24).

### Clinical manifestations

Genital warts are the most common clinical manifestation of genital HPV infection. They are warty, flat, dome-shaped, papillomatous, filiform, keratotic growths of normal skin color; rarely they are inflamed or hyperpigmented, and may affect any part of the skin or exposed mucous surfaces. Genital warts are most frequently found inside the preputium and frenulum, glans and coronary sulcus, on scrotum, inguinal folds, vulva, perineum, perianal and intraanal region, the vagina, cervix and urethra. More than 50% of women with GWs on the external genitalia have the same lesions in the vagina, whereas 20% of men with external lesions have intraurethral warts. Genital warts are frequently multifocal, especially in the intertriginous areas (macridation and maceration) (25, 26). A study of recent literature indicates a special entity - flat condyloma (lat. *Condylomata plana*), which used to be described as a clinical form of genital warts. They are commonly caused by HPV types 16, 18, 31, and 33. They are considered as an entity due to their higher oncogenic potential in regard to GWs (27, 28). Giant condyloma, or Buschke-Lowenstein tumor, is a massive tumorous lesion of the anogenital region, the size of a fist. Despite the impressive clinical picture, malignant transformations are rare. They are commonly caused by HPV types 6 and 11. It is believed that immunosuppression plays an important role in the pathogenesis of giant condylomas. In cases of clinical and histological malignancy, HPV types 16 and 18 were identified (29, 30, 31).

Another clinical manifestation of genital HPV infection also includes Bowenoid papulosis. This disease manifests as multiple hyperpigmented or hypopigmented papules, with histological signs of cellular atypia (similar to: Morbus Bowen; spinocellular carcinoma in situ). Lesions commonly contain HPV type 16 (29, 30, 31). Although usually asymptomatic, due to their location and size, GWs may cause pain, itching, urethral and vaginal bleeding, as well as urinary obstruction (25).

### Diagnosis and differential diagnosis

The diagnosis of GWs is based on the clinical presentation. A biopsy may be indicated if genital warts cannot be easily identified, in immunosuppressed patients, when response to therapy is unsatisfactory,

in cases when warts are pigmented, indurated, fixed, and ulcerated, but also in cases of high risk of malignancy (chronic GWs or positive Pap test) (32, 33). HPV infection is determined only by HPV DNA detection. The diagnosis is also made by polymerase chain reaction (PCR) and hybrid capture test (HC2). Serological tests with low sensitivity are useless (34). Application of 3-5% acetic acid is not recommended any more (false positive results) (9).

The differential diagnosis includes the following diseases and conditions: *condylomata lata*, seborrheic keratosis, dysplastic and benign nevi, *molluscum contagiosum*, *papillae coronae glandis*, Crohn's disease, lichen planus, *lichen nitidus* and malignant skin diseases (35).

## Therapy

There is no specific antiviral therapy for GWs. The therapy primarily involves the removal of visible lesions on the skin and mucous areas. If untreated, genital warts may grow larger and multiply, and about 95% of patients wish to undergo therapy. It is believed that therapy may induce natural regression of GWs. It remains unclear to what extent immunologic response affects and modifies the treatment, so it is impossible to predict relapses in treated patients. There is still no evidence that the treatment of GWs decreases the contagiousness of treated patients (36, 37). The matter of contagiousness opens another question: if subclinical infections should be treated or not. Clinical studies have shown that after laser therapy of subclinical infections, in women diagnosed by colposcopy, relapses occur in 88% of cases (38). It is still unclear whether patients with subclinical infections are as contagious as patients with clinical infections, but there is evidence that in many cases transmission to the partner occurs when there are no clinical signs or symptoms. According to the traditional clinical approach, treatment of genital warts in one partner does not affect the treatment outcome in the other (37).

Treatment of genital warts mostly includes medications and procedures targeting lesions and the immune system: 1) chemical agents (podophyllin, podophyllotoxin, imiquimod, trichloroacetic acid, 5-fluorouracil, interferon, cidofovir); 2) cryotherapy (liquid nitrogen or carbon dioxide snow); 3)

CO<sub>2</sub> laser; 4) photodynamic therapy; 5) surgical treatment (curettage, excision, electrocauterization, circumcision); 6) systemic and intralesional interferon therapy.

## Topical chemical agents

### Podophyllin

Podophyllin is a crude plant extract prepared by extracting the resin from the rhizome of Indian *Podophyllum emodi* or American *Podophyllum peltatum*. It induces tissue necrosis by blocking the cell mitosis. It is applied to genital warts as a 10-25% suspension in tincture, and it is removed by washing after 1 - 4 hours. It is usually applied once a week for at least 6 weeks. Due to its potential systemic toxicity causing bone marrow depression, its application is limited to less than 0.5 ml per less than 10 cm<sup>2</sup>. Podophyllin has teratogenic effects, whereas relapses occur in 40% of treated patients. It is least effective on the frenulum, scrotum and labia major in women (39). Studies also show that podophyllotoxin, a crude alcohol extract and a biologically active component in the podophyllum resin, is more effective than podophyllin and that it is taking its place in the treatment of GWs.

### Podophyllotoxin

Podophyllotoxin causes both epidermal and dermal necrosis by binding to cellular microtubules and by blocking mitotic activity in the metaphase. Podophyllotoxin is contraindicated in pregnancy. It is applied twice a day, three times a week, during 2 - 6 weeks. It is available in a 0.5% solution, cream or gel. In clinical practice, podophyllotoxin solution is used for penile lesions, while cream is used in women and for anal lesions. The maximum treatable surface area should not exceed 10 cm<sup>2</sup>. A complete remission is reported in 75% of cases treated with podophyllotoxin solution, and in 64.6% of cases treated with cream (8). Relapses occur in one third of patients after one month. Topical application of podophyllin and podophyllotoxin is associated with possible local adverse effects such as itching, pain, inflammation, edema and ulcerations (37, 39).

### Imiquimod

Imiquimod modifies the immune response and increases cellular indirect antiviral activity. However, imiquimod has no direct antiviral effects. Its effects proved better in women than in men, with complete

remission in 72% of treated women. Imiquimod 5% cream is used three times per week, during a 16 week period. The most frequent local adverse reaction is erythema (40). The reported relapse rate is lowest after three months – 9%, and highest after six months – 23% (41).

### **Trichloroacetic acid**

Trichloroacetic acid is used in an 80 – 90% solution. It has no systemic effect and it is safe for use during pregnancy. It is applied once a week. Its remission rate after six applications is 70%, while relapses occur in 36% of patients (42).

### **5-Fluorouracil**

5-Fluorouracil inhibits the nucleic acids synthesis. Due to its teratogenic effects, it is contraindicated during pregnancy. It is applied as a 5% cream on vulvar, perianal, penile and intrameatal genital warts. It is used 1 – 3 times a week, during 3 – 10 hours. It often causes local irritation (36, 39). Complete remission is reported in 41% of patients after 3 months, while relapses occur in 50% (43).

### **Interferon**

Interferon is a proinflammatory cytokine with antiviral effects. When combined with surgical or laser therapy, it causes complete remission of GWs in 54 – 62% of treated patients (44).

### **Cidofovir**

Cidofovir is a medication which was used for the treatment of cytomegalovirus and herpes virus infections, and later for GWs in HIV-positive patients. 1% cidofovir gel is applied once a day, for 5 days, during 6 two-week cycles. In immunocompetent patients complete remission is reported in 47% (44).

### **Cryotherapy**

Cryotherapy is a procedure in which a chemical, usually nitrous oxide or liquid nitrogen is used to freeze off genital warts. It causes both epidermal and dermal cellular necrosis, consequently leading to cessation of circulation in the tissues and edema. Cryotherapy is an effective and inexpensive method which is safe for use during pregnancy. Cryotherapy with liquid nitrogen is the most widely used method and it is applied with a cryo-spray. Another method includes application of liquid nitrogen or carbon dioxide snow using a cryo-probe for 10 – 20 seconds, freezing a wart and a margin of healthy skin. Generally, three sessions

are required, at intervals of 1 to 2 weeks. Anesthesia is rarely required for cryotherapy. Complete wart removal occurs in 79 – 88% of cases, while relapses occur in 25 – 39% (37, 39).

### **Laser therapy**

CO<sub>2</sub> laser therapy provides precision preserving the healthy tissue, especially in the treatment of extensive genital warts. It is used in the treatment of penile, anorectal and urethral GWs in men, and flat vaginal condylomas in women. It is safe to use during pregnancy. However, anesthesia is necessary. Complete wart clearance after CO<sub>2</sub> laser surgery has been reported in 23 – 52% of patients, while relapses occur in 60 – 77% of cases (36, 37, 39).

### **Photodynamic therapy**

By photodynamic (photochemical) therapy, 5-aminolevulinic acid is selectively accumulated in neoplastic and HPV-infected tissues and then activated by a red laser light. The result is tissue destruction (37).

### **Surgical treatment**

Surgical removal of GWs can be performed with a scalpel, scissors (scissor excision was first used for perianal and anal condylomas in 1978), or a curette in local anesthesia. It can be used during pregnancy, but there is a risk of infection. Regression occurs in 35 – 93% of patients, while relapses are reported in 19 – 29% (36, 37, 39). Electrosurgery is associated with a regression of 61 – 94%, whereas relapses occur in 14 – 22% of patients (45). In extensive and long-term GWs on the preputium, circumcision may be performed (45).

### **Systemic and intralesional interferon therapy**

Due to its high cost, bone marrow suppression, anaphylaxis, bronchospasm, fever, headache and myalgia, systemic use of interferon (3 million U sc or im 3 times/wk for 6 weeks) is neither primary, nor adjuvant therapy for GWs. Its efficacy varies from 7 – 82%, while relapses occur in 23% of treated patients (36, 39). Administration of intralesional interferon is associated with pain, because interferon is injected directly into the wart. Regression occurs in 35 – 53% of treated patients, whereas relapses occur in 21 – 25% of cases (39). Spontaneous resolution of genital warts in children is reported in more than 50% of cases. Drugs of choice are podophyllotoxin and imiquimod (46, 47).



### Combination therapy

High recurrence rate reported for monotherapy led to use of combination therapy (simultaneous or sequential application of two or more methods) with: CO<sub>2</sub> laser surgery and intralesional interferon therapy or imiquimod cream (48), intralesional interferon alpha 2b and podophyllin (49), electrocoagulation and 1% cidofovir gel (in HIV-positive patients) (49); trichloroacetic acid and podophyllin; trichloroacetic acid and cryotherapy; cryotherapy and podophyllotoxin; cryotherapy and imiquimod; surgical and imiquimod; podophyllin and imiquimod; trichloroacetic acid and podophyllin and cryotherapy; trichloroacetic acid and podophyllin and podophyllotoxin; trichloroacetic acid and podophyllin and imiquimod (3).

Although there are no sufficient data to make any conclusions, a combination therapy with podophyllin and cryotherapy induces complete clearance of GWs in 72.5% of patients after two treatment cycles, while after the same period of time combination of trichloroacetic acid and podophyllin shows regression of GWs in 62.3% of patients (Table 1) (50-53).

According to a recent cross-sectional survey, only 11% of all treatments involved a combination of two or more agents. However, the following combinations proved to be the most frequent initial choice of treatment: trichloroacetic acid and podophyllin, trichloroacetic acid and cryotherapy, cryotherapy and podophyllotoxin, cryotherapy and imiquimod (3).

Prevention of HPV infections is of great importance, not only to avoid transmission, but also to prevent HPV associated diseases, primarily cervical cancer. Considering the fact that prevention strategies are still not available, sexual abstinence is believed to be the only absolute primary prevention. Taking into account the above-mentioned HPV susceptibility to latent infection, secondary preventive strategies, such as treatment of GWs and cervical dysplasias, have not been found to be helpful. Complete protection from HPV infection is not possible, because infections may occur on sites not covered by the condom (54).

The quadrivalent prophylactic vaccine against HPV types 6, 11, 16 and 18 is the first successfully applied vaccine (55). Vaccination of children of both sexes, aged 10 – 13, would directly protect the immunized individuals, and indirectly protect their partners (56). Although this vaccine is not intended for treatment of GWs, the therapeutic vaccine HspE7, which consists of a fusion of the well known stimulator of cellular immunity, heat shock protein from *Mycobacterium bovis* and HPV 16E7 oncoprotein, given to patients with anal dysplasia, showed complete remission of GWs in 73% of patients 18 months after the first injection (57).

### Conclusions

Genital warts infection commonly occurs early in the sexual life of men and women. There is a strong relationship between GW infection and development

**Table 1.** Summary of reported results of combination therapy of genital warts

Treatment	Wart clearance	Recurrence	Reference
Trichloroacetic acid and podophyllin	53/85 (62.3%)	Not reported	Sherrard et al <sup>50</sup>
Podophyllin and cryotherapy	55/76 (72.5%)	Not reported	Sherrard et al <sup>50</sup>
Intralesional interferon and podophyllin	25/41 (61%)	67%	Douglas et al <sup>51</sup>
Systemic interferon and isotretinoin	40/44 (90.9%)	0%	Cardamakis et al <sup>52</sup>
Electrocauterization and cidofovir gel	19/19 (100%)	27%	Orlando et al <sup>53</sup>

of precancerous and cancerous lesions. There is no consensus about the treatment of GWs and there are many therapeutic options, but unfortunately no cure yet exists to prevent relapses. Vaccine has an important role in the prevention, and its application provides encouraging results in developing immunization strategies worldwide. A systematic and effective use of HPV vaccine should facilitate the implementation of universal immunization of persons of both sexes at the earliest age, not only of groups at risk. Until then, our task is to determine and apply the most effective methods of prophylactic treatment.

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## Genitalne bradavice - novi pristupi u lečenju

### Sažetak

Epidemiologija: Genitalne bradavice su klinička manifestacija infekcije humanim papilomavirusima sa prevalencijom od 1% kod seksualno aktivne populacije.

Etiologija i imunologija: Humani papilomavirusi su epitelio-epidermotropni. Čelijski imunološki sistem

ima glavnu ulogu u regresiji oboljenja uzrokovanih ovim virusima.

Kliničke manifestacije: Najčešća klinička manifestacija genitalne infekcije humanim papilomavirusima su genitalne bradavice. Ispoljavaju se u vidu bradavičastih formacija koje mogu biti: šiljaste (condylomata

acuminata), karfiolaste (eng. couliflower-shaped), kupaste (eng. dome-shaped), zaravnjene (condylomata plana) ili viseće (eng. pedunculated).

Dijagnoza i diferencijalna dijagnoza: Dijagnoza se najčešće postavlja na osnovu kliničke slike. Neposredno prisustvo virusa može da se dokaže jedino detekcijom HPV DNK.

Terapija: Za sada ne postoji specifično antivirusno lečenje. Terapija podrazumeva uklanjanje vidljivih

promena sa kože i sluznica. U lokalnoj destrukciji lezija, pored klasičnih hirurških metoda, primenjuju se različiti hemijski i fizički agensi, a u sistemske terapiji agensi koji deluju na imunološki sistem. Lečenje nije u svim slučajevima jednako efikasno i recidivi su za sada neizbežni. Alternativu monoterapiji čini, sve češće, kombinovana terapija. Važnu ulogu u prevenciji ima vakcina.