

## Genital Warts and Their Treatment

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**Genital warts are manifestations of a common viral sexually transmitted disease (STD) that are often diagnosed and treated with a variety of clinical specialties. Unlike for other STDs, there is a general lack of a well-established treatment algorithm for the management of external genital warts. This, coupled with a wide variety of treatments and clinical settings, makes the development of a simple algorithm virtually impossible. In this review what is known and not known about current treatments and case management will be discussed.**

Genital infection with human papillomavirus (HPV) is very common. Although the infection is usually asymptomatic, it is most frequently recognized as genital warts when symptoms are present. It has been estimated that ~1% of sexually active men and women in the United States have genital warts [1]. External genital warts (EGWs) are visible warts present on the external genital area.

Prior to initiation of treatment, accurate diagnosis is important. Since the diagnosis is based predominantly on physical examination, it is important for health care providers to understand the different morphological forms of EGWs as well as other conditions that can mimic or be mistaken for EGWs.

Once the diagnosis has been established, there are a variety of patient-applied and provider-administered treatments. Unfortunately, not all modalities are always available in all clinical settings, and not all have been well studied. Effective treatment is dependent upon an understanding of the disease and treatment options. Recurrence following treatment appears to be a common event that further confounds case management.

In addition to treatment of EGWs, patients and their partners need to be educated about what is known and unknown about EGWs and the relationship between HPV infection and genital cancers. Clinicians treating patients with EGWs need to establish consistent policies about cervical cancer screening and better understand relations between EGWs and anal cancer.

This review will focus primarily on available treatments and, in brief, HPV screening issues as they relate to patients with EGWs and their sex partners. In contrast to bacterial sexually transmissible diseases (STDs), for which traditional goals of therapy are elimination of symptoms, prevention of associated morbidity and long-term sequelae, and interruption of transmission through eradication of infection, the treatment and public health goals for viral STDs have been less clear. While this lack of clarity can be a source of frustration for clinicians and patients, there are a number of goals that can be met in the treatment of EGWs.

### Diagnostic Considerations

HPV is a nonenveloped, double-stranded DNA virus that infects epithelial tissues and causes a spectrum of disease ranging from asymptomatic infection to warts, precancerous changes, and malignancy. There are at least 70 HPV genotypes, a number of which are recognized in the genital epithelium, most commonly HPV 6, 11, 16, 18, 31, and 35 [2–8]. Although some HPV types are considered “high risk” types on the basis of their association with anogenital cancer (e.g., HPV 16 and 18), many are associated with cancer only rarely, if at all, and are considered “low risk” types (e.g., HPV 6 and 11) [8].

The association between high-risk oncogenic HPV types and invasive cervical cancer is strong, and high-risk oncogenic HPV types are found in Pap smears showing cervical dysplasia [9, 10]. When low-risk HPV infections of the genital tract become symptomatic, the infected keratinocytes proliferate in an abnormal fashion and produce genital warts [1]. A very rare expression of low-risk, external genital HPV infection is the Buschke-Lowenstein tumor, a form of verrucous squamous cell carcinoma [11, 12].

*External genital warts.* EGWs are visible warts that occur in the genital area (i.e., penis, scrotum, vulva, perineal area,

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perianal area, pubic area, and crural folds) [13–16]. They may occur as one or more discrete lesions or coalesce into confluent plaques [17–19].

The HPV types that cause EGWs can also cause warts in the vagina, on the uterine cervix, and inside both the urethra and the anus [20–22]. Intra-anal warts are seen most often in patients who have had anoreceptive intercourse and are distinct from perianal warts [16]. Outside the genital area, these HPV types have been associated with conjunctival, nasal, oral, and laryngeal warts.

HPV infection is highly prevalent, occurring in as many as 20% to 40% of sexually active adults [23–25]. Many, if not most, low-risk and high-risk HPV infections are never clinically expressed or diagnosed as disease. Infections with low- and high-risk HPV types can regress spontaneously and do not necessarily produce EGWs or malignancies [26]. Though young age is more often associated with spontaneous regression and immunosuppression is associated with persistence, other factors that affect regression or persistence have not been clearly defined.

There are four morphological types of genital warts: (1) condylomata acuminata that have the shape of cauliflower; (2) smooth papular warts that are dome-shaped, usually skin-colored, 1–4-mm papules; (3) keratotic genital warts that have a thick, horny layer and may resemble common warts or seborrheic keratosis; and (4) flat warts that are flat to slightly raised, flat-topped papules. The morphological type of the EGW may be influenced partially by the type of skin affected. Two major types of skin in the genital area include fully keratinized hair-bearing or non-hair-bearing skin and partially keratinized non-hair-bearing skin. The latter surface is often mistakenly referred to as mucous membranes because it is smooth and moist, a feature due to the thin stratum corneum. The condyloma acuminatum type of genital wart tends to occur on moist surfaces, the keratotic and smooth papular types occur on fully keratinized skin, and flat warts can occur on either surface.

The diagnosis of EGWs in the immunocompetent patient is based primarily on visual examination, which can be aided by bright light and magnification. Generally, EGWs can be visualized without instrumentation, and clinical diagnosis has been shown to be reliable and consistent with the histologic diagnosis of EGW disease [20, 27–31]. Some clinicians find bright light and a hand lens, a magnifying loop, or a colposcope helpful in identifying EGWs. Though colposcopy and urethroscopy are beneficial in some specialty practices, they are not indicated for general practice. The “acetowhite test,” a whitening of HPV-infected tissues that is produced after brief soaking with mild (3%–10%) acetic acid solutions, is not routinely recommended [32–35]. The acetowhite test is not a highly specific diagnostic tool and in many patient populations has a low positive predictive value.

The differential diagnosis of EGWs includes normal anatomic structures (e.g., pearly penile papules [36], vestibular papillae, and sebaceous [Tyson’s] glands) [36] as well as ac-

quired conditions such as molluscum contagiosum [37], Crohn’s disease, seborrheic keratosis [38], lichen planus [39], lichen nitidus, skin tags [38, 40], melanocytic nevi, pseudo-verrucous papules [35] and condyloma lata, Bowenoid papulosis, vulvar intraepithelial neoplasia (in women) [41], and Buschke-Lowenstein tumor [10, 11].

Simple biopsy is seldom needed but may enhance diagnosis and should be considered when (1) the lesions are atypical; (2) the diagnosis is in doubt; (3) there is progression of disease during treatment; (4) there are prompt and/or frequent recurrences; (5) warts are pigmented, indurated, ulcerated, or fixed to underlying structures; or (6) there are individual warts larger than 1 cm (suggestive of Buschke-Lowenstein growths). Since EGWs can be multifocal, it may be useful to examine the entire genital area to identify all EGWs prior to treatment [42].

Diagnosing and treating EGWs in the immunocompromised patient are more challenging. Currently, patients who present with any STD should be counseled and evaluated for HIV infection. For those found to be infected, as well as patients who present with immunodeficiency caused by other conditions (e.g., transplantation), biopsy may more often be required to discriminate between EGWs and high-grade squamous intraepithelial lesions. In addition, the course of treatment may be longer for the immunocompromised patient and the recurrence of disease more likely than for immunocompetent patients.

The use of HPV detection and typing in the diagnosis and treatment of EGWs has not yet been defined. It has been clearly demonstrated that routine genital warts are predominantly due to HPV type 6 and less commonly to HPV type 11 [8, 43, 44]. Sexually active patients with or without EGWs may also harbor a variety of other low- and high-risk HPV types. Because the diagnosis, treatment, and management of EGWs are not influenced by HPV type, routine HPV detection and typing for EGWs is not currently recommended.

*Vaginal warts.* Like other genital warts, those that occur in the vagina are caused by HPV infection, and the goal of therapy is wart eradication when the warts are causing or likely to cause symptoms.

*Urethral-meatal warts.* Genital warts located in the urethral meatus are usually caused by low-risk oncogenic HPV types, and like that for EGWs, the goal of therapy is eradication of symptomatic warts.

*Intra-anal warts.* Intra-anal warts are distinct from perianal EGWs and are most common among men and women who engage in anoreceptive intercourse [45]. HPV infection has been associated with anal and rectal squamous cell carcinoma [45, 46]. Unfortunately, the natural history of intra-anal HPV infection is unclear, and there are currently no guidelines for anal cancer screening.

*Oral warts.* Patients may not be aware that warts in the oral cavity may be sexually transmitted. Consequently, though their occurrence is infrequent, all patients being evaluated for EGWs or cervical, vaginal, or intra-anal warts should be queried about oral symptoms such as new growths and should be examined for oral warts [47].

## Treatment

*External genital warts.* The primary goal of treatment of EGWs is to eliminate warts that cause physical or emotional symptoms or distress. EGWs are usually asymptomatic but can be painful, friable, or pruritic and, depending upon their size and anatomic location, may interfere with normal function. Moreover, EGWs may be socially stigmatizing and a troubling reminder of an STD. Available treatments for EGWs may or may not cure the underlying HPV infection, and though treatment can induce wart-free periods, HPV infection may be persistent. In addition, though persons with EGWs can transmit genital wart disease to their sex partners, eliminating warts may or may not decrease infectivity because EGWs may not represent the only site of HPV infection.

If left untreated, EGWs may resolve on their own, remain unchanged, or increase in size or number; they rarely become malignant [20, 26, 48, 49]. While a few large clinical trials showed that EGWs in as many as 28% of patients treated with placebo alone spontaneously regressed, other investigators have reported no spontaneous regressions under similar circumstances. Predictors of EGWs that remain unchanged for prolonged periods have not been described and are poorly understood. Pregnancy and immune deficiency (e.g., due to posttransplantation immune suppression and HIV infection) are associated with larger or more numerous EGWs.

Treatment plans should include a thorough physical and psychosocial assessment as well as a consideration of the available medical resources of the clinician, the patient, and the community. No single treatment has been found to be ideal for all patients or all warts, and most treatments appear to have comparable efficacy. The size, anatomic location, number, and character of the EGWs will affect treatment decisions, as will coexisting medical conditions such as pregnancy and immune deficiency. The cognitive and developmental state of patients influences whether self-applied therapies can be used safely and effectively.

Most current EGW treatments can disrupt skin integrity to varying degrees and for varying durations, a factor that will affect patient-care decisions. The presence of healing, open wounds may increase a patient's risk of acquiring or transmitting certain STDs.

The typical patient has a relatively small number of EGWs that can be eliminated eventually by one or more treatment modalities (table 1) [50]. Most treatments can be classified broadly as patient-applied or provider-administered. Clinicians who treat patients with EGWs should be knowledgeable about interventions and have more than one available; preferably, at least one should be a patient-applied treatment [34]. Many patients will require a course of therapy rather than a single treatment.

Patient-applied therapeutic agents (e.g., podofilox [Condylox, Oclassen Pharmaceuticals, Corona, CA] or imiquimod [Aldara, 3M Pharmaceuticals, St. Paul]) may best suit the needs of those who desire more control over their care or a less-

**Table 1.** Treatments for external genital warts.

Type	Agent or therapy	
Patient-applied topical	Podofilox 0.5% solution or gel (Condylox)*	
	Imiquimod 5% cream (Aldara) <sup>†</sup>	
	5-Fluorouracil cream	
	Cidofovir (HPMPC: [S]-1-[3-hydroxy-2-phosphonylmethoxypropyl]cytosine)	
Provider-prescribed or -applied	Topical	Cryotherapy
		Podophyllin (10%–25% compound)
		Trichloroacetic acid (80%–90%) Bichloroacetic acid (80%–90%)
	Intralesional injectable	Interferon
	Systemic	Interferon
	Office surgery	Electrosurgery
		Curettage
		Tangential scissor excision
		Tangential scalpel excision
	Other surgery	Laser

\* Oclassen Pharmaceuticals, Corona, CA.

<sup>†</sup> 3M Pharmaceuticals, St. Paul.

invasive form of treatment. However, before prescribing these agents, providers have a special responsibility to assess whether patients who use these agents have adequate cognitive ability to follow therapeutic directives and whether they can successfully identify and reach the warts they are to treat.

Provider-administered treatments include cryotherapy and use of trichloroacetic acid (TCA), bichloroacetic acid (BCA), or podophyllin resin. Curettage, electrosurgery, and fine-scissor excision are simple office-based procedures that are used to remove warts.

More complex destructive methods that are used alternatively to treat EGWs include laser therapy and intralesional administration of interferon. These modalities are for patients who are not candidates for other treatments. It has been found that systemic (injectable) interferon is not efficacious for EGWs.

There are no clear patient-treatment guidelines that specify what treatment to use first or when to change therapeutic modalities or refer patients to other, more specialized practitioners. However, experts suggest that treatments should be changed or referral to more experienced clinicians should occur when: (1) three treatment sessions have passed without significant improvement, (2) complete clearance has not occurred after six treatment sessions, or (3) continued treatment would extend beyond a manufacturer's recommendations for patient-applied therapies [34]. Most important, clinicians should monitor patients' progress closely and avoid overtreatment [34]. It is important that the treatment not be significantly worse than the disease.

Side effects associated with all therapeutic modalities vary. Local reactions are common with most treatments, and the incidence and severity of ulceration and erosion vary across

treatments and within modalities relative to the dose of medication or the method applied. While persistent hypopigmentation or hyperpigmentation is a common complication of ablative modalities, depressed or hypertrophic scars occur rarely [51, 52]. In addition, treatment can result in disabling chronic pain syndrome (e.g., vulvodynia) or hypoesthesia at the treatment site, and patients with fair complexions may be the most susceptible to chronic pain syndromes [51, 53].

### Patient-Applied Treatments

*Podofilox (Condylox) solution and gel preparations.* Podofilox (Condylox) solution or gel is a patient-applied product that is antimitotic, causes localized tissue necrosis, and destroys warts [54]. Localized epidermal pallor, caused by intracellular and intercellular edema, can usually be seen within 48 hours of application [55]. Podofilox solution or gel is dispensed in 0.5% concentrations and does not contain the mutagenic flavonoid compounds (quercetin and kaempferol) that are found in the provider-applied analogue, podophyllin [56]. Podofilox solution has been extensively evaluated in randomized and placebo-controlled clinical trials [19, 50, 54, 57–64].

Placebo-controlled studies show that between 45% and 82% of patients attain total clearance within 4–6 weeks of treatment, and randomized comparison studies show that between zero and 91% of patients have recurrences (table 2a) [16, 18, 20, 22, 51, 54, 57, 59, 61, 65–68, 71–74]. Podofilox is not recommended for internal use or for patients with known hypersensitivity to its ingredients. Podofilox is recommended for use on wart areas of  $\leq 10$  cm<sup>2</sup> [34]. Adverse effects associated with podofilox include skin ulceration and erosions, erythema, and irritation; phimosis; and preputial tightening, pain, burning, and soreness (table 2a) [16, 18, 20, 22, 51, 54, 57, 59, 61, 65–68, 71–74].

Podofilox gel, thought to be an easier-applied alternative to the solution preparations, has recently been evaluated in a double-blind, vehicle-controlled study of 326 men and women [69]. Approximately 45% of all patients treated with the 0.5% gel showed complete wart clearance within 8 weeks [69].

*Imiquimod (Aldara).* Imiquimod, 1-(2-methylpropyl)-1H-imidazo[4,5C]quinolin-4-amine, is a patient-applied, topically active, nonnucleoside heterocyclic amine, immune-response-enhancing agent [75, 76]. It is a potent inducer of interferon- $\alpha$  and other cytokines, including tumor necrosis factor- $\alpha$  and IL-6 [75, 76]. Randomized, placebo-controlled, multicenter safety and efficacy studies have been performed on 1% and 5% cream preparations and show that 5% preparations are about twice as effective as the 1% creams (table 2b) [79]. Overall, between 37% and 85% of patients treated with 5% cream were wart-free after therapy, and 13%–19% had recurrences during the follow-up period (table 2b) [75–77, 79, 80]. Localized burning, erythema, irritation, pain and tenderness, and ulcerations have been reported as adverse reactions to imiquimod and may be related to the direct therapeutic action of the agent (table 2b) [75, 80].

### Provider-Administered Treatments

*Cryotherapy.* Cryotherapy causes cryocytolysis, resulting in tissue sloughing and wart destruction. Efficacy studies have been limited to case-series studies and randomized studies that contrast cryotherapy with other standard treatments and have shown that between 60% and 97% of patients treated remained wart-free 3–6 weeks after treatment (table 2c) [27, 63, 64, 81–88]. Wart recurrence has been reported to occur in 20%–79% of patients participating in clinical studies.

Though there is no real patient-related contraindication for cryotherapy other than cryoglobulinemia, it does require training, without which warts are frequently overtreated or undertreated, leading to poor efficacy and increased complications. Pain and necrosis following application of the liquid nitrogen are fairly universal, and blistering sometimes occurs. Although the use of injected local or topical anesthesia is not necessary, it can facilitate cryotherapy, particularly when a large number or area of warts is present. Topical anesthetic in the form of a eutectic mixture of prilocaine and lidocaine can be used for this purpose. Adverse effects include balanoposthitis, irritation, local edema, necrosis, ulceration, and pain, especially when the treated area thaws.

Effective cryotherapy is achieved with use of spray application, cryoprobe, or loosely wound cotton on a wooden applicator, but not with a tightly wound, typical cotton swab. In general, cryotherapy is effective for dry and moist warts. However, extensive cryotherapy, treating large warts or large areas or numbers of warts at one time, can create some wound care problems.

*Podophyllin.* Podophyllin resin has been evaluated extensively in randomized treatment-comparison studies in human populations. It is usually compounded as a 10%–25% suspension in tincture of benzoin and contains a number of antimitotic lignans, including podofilox [23, 50, 54, 57–59, 84, 89]. Epidermal pallor usually develops within 48 hours of application because of the intracellular and intercellular edema associated with necrosis in the affected tissues [55]. Podophyllin resin preparations vary greatly in their concentration of active components and contaminants, such as known mutagens. The shelf life and stability of podophyllin resin are unknown, and well-standardized preparations are not available.

It is important to apply a thin layer of podophyllin resin to the warts and allow it to air-dry completely before the patient assumes a normal sitting or standing position. Overapplication or failure to air-dry can result in the spread of the compound and a significant local reaction. Tincture of benzoin localizes the treatment to the affected tissues and is water-insoluble. When it is properly applied, there is no need to protect surrounding skin with petrolatum or other barriers. While patients are advised routinely to wash the treated area 1–4 hours after the application, the source of this recommendation is uncertain and the practice may not always be necessary.

Studies show that warts clear completely for 19%–80% of patients treated with podophyllin (table 2d). There is no evi-

dence that administration of podophyllin greatly enhances other therapeutic interventions when used as an adjunct therapy, and between 23% and nearly 70% of patients whose warts clear have recurrent EGWs [19, 23, 26, 50, 57–59, 89–91]. Hypersensitivity to product ingredient contraindicates use, and podophyllin is not recommended for pregnant women.

Podophyllin is recommended for use on wart areas of  $\leq 10$  cm<sup>2</sup>, as use on larger surface areas will increase absorption and may induce toxicity. Though the active agent, podophyllum resin, is not a mutagen, the suspension does contain carcinogens, including flavonoids, quercetin, and kaempferol [65]. Side effects associated with podophyllin include skin ulceration, erythema, and irritation; phimosis; and preputial tightening, pain, burning, and soreness (table 2d) [23, 50, 54, 57, 59, 61, 84].

**TCA/BCA.** TCA and BCA are caustic agents that destroy warts by chemical coagulation of proteins [28, 81, 88, 92]. TCA/BCA solutions have a very low viscosity (comparable to that of water) and, if overapplied, can spread rapidly and “run,” damaging a significant area of adjacent normal tissue. TCA/BCA solutions should be applied sparingly and allowed to dry before the patient sits or stands and are most effective for small warts on moist surfaces. If there is intense pain, the acid can be neutralized with soap and sodium bicarbonate.

TCA/BCA solutions are widely used but rarely studied. Randomized comparison studies and descriptive case-series studies have revealed clearance rates of between 50% and 100% (table 2e and 2f) [28, 81, 88, 92]. Only two published study reports described recurrence rates among patients treated with TCA/BCA, and they showed that between 6% and 50% may develop recurrent EGWs. Treatment solution concentrations as described in the literature are not standardized, and concentrations of 85%–95% have been reported [81, 92]. Skin ulcerations, erosions, erythema, and irritation, as well as pain, burning, and soreness, are adverse side effects associated with this treatment; one study reported the use of suprapubic catheterization in seven and pyelonephritis in one of 32 treated women [88, 92].

**Surgical removal.** EGWs can be physically destroyed by curettage and electrocautery or tangentially excised with fine scissors or a scalpel. Surgically removing warts is advantageous because it renders the patient wart-free, usually in a single visit. Conversely, the disadvantage is that significant training, a moderate amount of equipment, and a longer patient visit are required. Simple in-office surgical excision requires local anesthesia.

Although surgery is obviously of most benefit when EGWs are present in large numbers or over large surface areas, it can also be used for average cases. While the cost of a single surgical visit may be greater, surgery can accomplish in one visit what other ablative modalities often require multiple visits to accomplish, which results in greater cost-effectiveness.

**Electrocautery/electrotherapy.** Once anesthesia is attained, the EGW(s) can be physically destroyed by electrocautery or thermal coagulation, and no additional hemostasis is required. Electrocautery thermally disrupts EGWs and coagulates proteins of treated tissues.

Reports of a randomized comparison study and several comparative case-series have suggested that electrocautery may be as effective as cryotherapy (table 2g) [24, 25, 64, 93]. Studies showed that local pain and possible infection may be side effects of electrocautery, and in one study 22% of patients whose warts cleared had recurrences [64]. Like cryotherapy, electrocautery requires advanced training to prevent undertreatment or overtreatment of the affected area.

**Curettage and tangential surgical excision.** Curettage and scissor and scalpel excision directly remove genital warts. Since most warts are exophytic, this can be accomplished so that the resulting wound extends only into the upper dermis. Hemostasis can be achieved with an electrosurgical unit or a chemical styptic, e.g., aluminum chloride solution or Monsel's solution; suturing is rarely required or indicated when removal is done properly.

Randomized treatment comparison studies and descriptive case-series studies have examined the efficacy of surgical excision and have shown nearly complete eradication within 1–6 weeks of treatment and recurrence rates of between 8% and 35% within 1 year of treatment [23, 52, 62, 94]. There are no reported contraindications for scissor/scalpel excision, with the exception of a known bleeding abnormality. Localized pain, for which mild analgesics may be required, and bleeding are side effects associated with this treatment, and should operating-room surgery be required (which is rare), all of the associated hazards of general anesthesia apply [23, 52, 62, 94].

#### Alternative Treatment Methods

Complex ablative therapies are more costly and require expensive equipment and more specialized training for proper execution. They also sometimes require general anesthesia, and side effects may be more common among these modalities. Laser therapy and other surgical modalities may be more appropriate for patients who present with large treatment areas.

**Laser excision.** Laser vaporization usually requires local anesthesia but may, when the treatment field is wide or the patient is very young, require general anesthesia. Attention to surgical planes is important to avoid scarring [95, 96]. Once anesthesia is achieved, the EGWs can be physically destroyed. In most circumstances, no additional hemostasis is required. Since most warts are exophytic, the resulting wound usually extends only into the upper dermis if proper power settings are used.

Most studies examining laser treatment have used convenience sampling and could not adequately control for possible confounding variables. A further complication is that three of the four reported randomized studies also evaluated adjunct therapies (table 2h) [14, 15, 47, 52, 61, 92, 97–102]. Laser therapy shows an immediate effectiveness at rates of 60%–100%, though, as with other modalities, efficacy statistics may be dependent upon the time elapsed between treatment and assessment, the number of treatments required to initially clear

**Table 2.** Data from studies of treatments for genital warts.

Agent or therapy studied, reference(s)	No. and sex of patients enrolled/ no. analyzed	Design	Regimen (no. of recipients)	Clearance rate (%) at indicated time	
				First assessment at/ after end of treatment	Further assessment(s)
(a) Podophyllotoxin (podofilox, or PDX)					
[59]	60/55 F	O, R	PD 20%: 1×/w (27) PDX 0.5%: 2×/d, 3 d/w, for 4 w (28)	4 w: PD: 59 (16/27) PDX: 82 (23/28)	3 mo: PD: 48 (13/27) PDX: 71 (20/28)
[54]	252/200 (133 M, 67 F)	O, R	PD 25%: 2×/w for 5 w PDX 0.5%: 2×/d, 3 d/w, for 5 w	1 w: PD M: 19% (7/36) F: 19% (5/26) PDX: M: 53% (51/97) F: 37% (15/41)	5 w: PD M: 72% (26/36) F*: 62% (16/26) PDX: M: 86% (83/97) F*: 78% (32/41)
[65]	46 M	Observer-blind, R	PDX 0.5% sol: 2×/d, 3 d/w, for 2–4 cycles (24) PDX 0.5% cream: 2×/d, 3 d/w, for 2–4 cycles (22)	2 w after final tx: PDX sol: 95% (23/24) PDX cream: 63% (14/22)	12 w: PDX sol: 63% (15/24) PDX cream: 63% (14/22)
[66]	90 M	R, O	PDX 0.15% cream: 2×/d, 3 d/w, for ≤4 cycles (30) PDX 0.3% cream: 2×/d, 3 d/w, for ≤4 cycles (31) PDX 0.5% sol: 2×/d, 3 d/w, for ≤4 cycles (29)	1 <sup>st</sup> Cycle: 0.15%: 37% (11/30) 0.3%: 45% (14/31) 0.5%: 52% (15/29)	4 <sup>th</sup> Cycle: 0.15%: 70% (21/30) 0.3%: 81% (25/31) 0.5%: 63% (24/29)
[67]	60 M	O, R, Comp	PDX 0.15% cream: 2×/d, 3 d/w, for ≤4 cycles (20) PDX 0.3% cream: 2×/d, 3 d/w, for ≤4 cycles (20) PDX 0.3% sol: 2×/d, 3 d/w, for ≤4 cycles (20)	4 w: 0.15%: 70% (14/20) 0.3% cream: 100% (20/20) 0.3% sol: 100% (20/20)	
[68]	80 F	DB, PC, R	PDX 0.3% cream: 2×/d, 3 d/w, for ≤4 cycles (30) PDX 0.5% cream: 2×/d, 3 d/w, for ≤4 cycles (30) PBO: 2×/d, 3 d/w, for ≤4 cycles (20)	4 w: 0.3%: 53% (16/30) 0.5% 83% (25/30) PBO: 0% (0/20)	
[16]	60 M	DB, PC, R	IFN-α cream, 2 MU/g: 3×/d, 3 d/w, for 4 w (20) PDX 0.5% cream: 3×/d, 3 d/w, for 4 w (20) PBO (matching cream): 3×/d, 3 d/w, for 4 w (20) For treatment failure at 4 w: cycle could be repeated for 3 w	End of treatment (~4 w): IFN: 90% (18/20) PDX: 60% (12/20) PBO: 20% (4/20)	
[69]	326 (194 M, 132 F)/316	DB, VC, R	0.5% PDX: 2×/d for 3 d for ≤8 w (213) Vehicle: 2×/d for 3 d for ≤8 w (103)	4 w: PDX: 37% (62/167) Vehicle: 2% (2/86)	8 w: PDX: ~45% (81/181) Vehicle: 4% (4/98)

**Table 2.** (Continued)

Recurrence rate	Adverse experience(s)	Other
3 mo: PD: 19 (3/16) PDX: 13 (3/23)	Local (PD/PDX): tenderness (20/18), burning (19/22), pain (17/18), erythema/erosion (1/7)	An inclusion criterion was wart size of <5 mm
13 w: PD M: 50% (5/10) F: 43% (3/7) PDX: M: 18% (7/37) F: 24% (5/21) PDX sol: 35% (8/23) PDX cream: 0% (0/14)	Local: tenderness, burning or pain, erythema, edema, erosions; highest incidence occurred at 1 w  Local: Mild to moderate adverse reactions in 35% with PDX sol vs. 40% with PDX cream	Study protocol initially divided PDX group into 2 study groups, collapsed into 1 group for analysis; many lost to f/u at 13 w  Separate analysis of tenderness, burning, pain, erythema, erosions, and edema did not show differences between the two treatment groups. No. of warts: 1–5, 16%; 6–10, 33%; 11–50, 42%; >50, 9%.
16 w: 0.15%: 13% (4/31) 0.3%: 19% (6/30) 0.5%: 17% (5/29)	Local (0.15%/0.3%/0.5%): itching, burning, tenderness, pruritus, erythema, erosion; mild to moderate in most but severe in a few (2/5/5)	
16 w: 6% (3/54)	Local: mild to moderate erythema (18), pruritus (18), burning sensation (18)	Representative bx specimens: histology/Southern blot, 90% HPV-6/11-positive
16 w: 0.3%: 14% (3/16) 0.5%: 4% (1/25) PBO: 0	Local: tenderness (23), burning (14)	Representative bx specimens: histology/Southern blot: 90% HPV-6/11 positive; cure was bx-proven (if cured, no further tx after bx)
1 y: 2/34 (treatment group unspecified)	IFN, systemic: flu-like symptoms were reported to be rare; local: mild localized tenderness, burning sensation, and fever with headache and itching, which normalized within 24 h (9); laboratory: leukopenia was rare	Bx prior to acetowhite test; Southern blot: 82% positive for 6 or 11 types of HPV; 18% HPV-negative, but histology showed koilocytotic atypia; bx confirmed regression test for cure; 43% (26/60) had lesions on labia majora/minora, 22% (13/60) on introitus, 17% (10/60) on perianal area, 12% (7/60) on perineum, 8% (25/60) on clitoris; lesion bx findings: 66% (213/322) were condyloma acuminatum, 27% (86/322) were papules, and 7% (23/322) were macules; maximum clearance occurred in w 3–4
	Local (% M/F): PDX: inflammation (52/82), erosion (41/61), pain (56/50), burning (77/71), itching (61/53), bleeding (33/27) Vehicle: inflammation (12/10), erosion (0/5), pain (10/3), burning (63/34), itching (37/16), bleeding (3/2)	An inclusion criterion was $\geq 2$ external anogenital warts; postmenopausal women had one lesion biopsied and screened to confirm diagnosis; mean no. of warts, 5.45; mean total wart surface area (mm <sup>2</sup> ), 150.5; mean duration of infection, 25.7 mo

NOTE. BCA = bichloroacetic acid; bx = biopsy; Comp = comparative; cryo = cryotherapy; DB = double-blind; EGWs = extragenital warts; epi = epinephrine; f/u = follow-up; 5-FU = 5-fluorouracil; HPMPC = cidofovir; HPV = human papillomavirus; IFN = interferon; O = open; PBO = placebo; PC = placebo-controlled; PD = podophyllin; PDX = podofilox; R = randomized; Sol = solution; TCA = trichloroacetic acid; tx = treatment(s); VC = vehicle-controlled.

\* Data for 5-w assessment not reported; "clearance of all warts at some time during the treatment period."

**Table 2.** (Continued)

Agent or therapy studied, reference(s)	No. and sex of patients enrolled/ no. analyzed	Design	Regimen (no. of recipients)	Clearance rate (%) at indicated time	
				First assessment at/ after end of treatment	Further assessment(s)
[70]	60/56 F	R, DB, PC	PDX 0.5%: 2×/d, 3 d/w, for ≤3 cycles (48) PBO: 2×/d, 3 d/w, for ≤3 cycles (12)	1 w: PDX: 41% (18/44) PBO: 0% (0/12) 3 w: PDX: 91% (40/44) PBO: 8% (1/12)	3 mo: PDX: 77% (34/44)
[18]	57/51 M	DB, PC, R	PDX 0.25%: 2×/d for 3 d for ≤2 cycles (18) PDX 0.5%: 2×/d for 3 d for ≤2 cycles (16) PBO: 2×/d for 3 d for ≤2 cycles (17)	End of tx: 0.25%: 72% (13/ 18) 0.5%: 81% (13/16) PBO: 0% (0/17)	5–7 w: 0.25%: 63% (5/8) 0.5%: 83% (10/12) 0% 20–23 w: 0.25%: 40% (2/5) 0.5%: 80% (7/8)
(b) Imiquimod (1-[2-methylpropyl]- 1h-imidazo[4,5 C]quinolin-4- amine) [77]	Trial 1, 108; trial 2, 311	DB, PC, R	Trial 1 (108), 5% imiquimod cream: 3×/w for ≤8 w PBO vehicle cream: 3×/w for ≤8 w Trial 2 (311), 5% imiquimod cream: 3×/w for ≤16 w (109) 1% Imiquimod cream: 3×/ w for ≤16 w (102) PBO vehicle cream: 3×/w for ≤16 w (100)	8 w: Trial 1: 5%: 40% PBO: 0% 16 w: Trial 2: 5%: 56% 1%: 27% PBO: 14%	
[75]	108	DB, PC, R	5% Imiquimod cream: 3×/ d for ≤8 w (51) PBO cream: 3×/d for ≤8 w (57)	Imiquimod: 37% (19/51) PBO cream: 0% (0/57)	
[78]	311	DB, R, PC	1% Imiquimod cream: 1×/ d, 3×/w, for ≤16 w (109) 5% Imiquimod cream: 1×/ d, 3×/w, for ≤16 w (102) PBO vehicle cream: 1×/d, 3×/w, for ≤16 w (100)	1%: 27% 5%: 56% PBO vehicle: 14%	
[76]	311/234	DB, R, PC	5% Imiquimod: 3×/w for ≤16 w 1% Imiquimod: 3×/w for ≤16 w PBO vehicle cream: 3×/w for ≤16 w	8 w: 5%: 25%	End of treatment: 5%: 56% 1%: 27% PBO: 14%
(c) Cryotherapy (cryo) [81]	86/86	R	Cryo with pledget: 1×/w for ≤6 w (53) TCA 95%: 1×/w for ≤6 w (33)	≤6 w: Cryo: 70% (37/53) TCA: 64% (21/33)	3 mo: Cryo: 86% (37/43) TCA: 70% (21/30)

**Table 2.** (Continued)

Recurrence rate	Adverse experience(s)	Other
3 mo: PDX: 15% (6/40) PBO: not specified	PDX: moderate burning (48%), pain/tenderness (41%), erosion (5%). PBO: mild burning (27%), pain/burning (14%), erosion (43%)	Exclusion criterion: condylomata in the vagina, cervix, or anal area; recurrences in women without prior tx, 8% (2/24)
33% (9/24)	Erythema, tenderness, and/or erosions were mild (13), moderate (3), or pronounced (6); itching and/or burning was mild (16), moderate (2), or pronounced (5)	Of the 9 recurrences, 3 were at the tx site and 4 were at mixed (tx and new) sites; previously untreated penile warts were noted; mean no. of warts: PBO = 7.8, 0.25% PDX = 12.1, and 0.5% PDX = 8.4
10 w: Trial 1: 5%: 19% PBO: no clearance		Pairwise comparison for both M and F showed 5% > 1% ( $P = .0001$ ), 5% > PBO ( $P < .001$ ), 1% not statistically different from PBO
12 w: Trial 2: 5%: 13% 1%: 0% PBO: 10%		
10 w: 19% (3/16)	Local: itching (26), erythema (16), burning (15), irritation (8), tenderness (5), ulceration (5), pain (4)  During f/u period: 1%, 0; 5%, 13%; PBO, 10%	F/u of patients with total clearance, $\leq 10$ w  Pairwise comparisons of 1% and 5% cream showed 5% imiquimod had a significantly higher clearance rate ( $P = .0001$ )
5%: 13% (6/45) 1%: 0% (0/18) PBO: 10% (1/10)	Local (5%/1%/PBO): inflammation and erythema (67%/26%/24%)  TCA: ulcerations (9)	Exclusion criteria: positive Pap smear and colposcopic evidence of high-grade squamous intraepithelial lesions; % with total clearance due to 5% imiquimod: F, 77%, and M, 40%; development of new warts during study (5%/1%/PBO): 31%(33/109)/42%/41%  Newly diagnosed EGWs; gender differences in the efficacy of tx

NOTE. BCA = bichloroacetic acid; bx = biopsy; Comp = comparative; cryo = cryotherapy; DB = double-blind; EGWs = extragenital warts; epi = epinephrine; f/u = follow-up; 5-FU = 5-fluorouracil; HPMPc = cidofovir; HPV = human papillomavirus; IFN = interferon; O = open; PBO = placebo; PC = placebo-controlled; PD = podophyllin; PDX = podofilox; R = randomized; Sol = solution; TCA = trichloroacetic acid; tx = treatment(s); VC = vehicle-controlled.

\* Data for 5-w assessment not reported; "clearance of all warts at some time during the treatment period."

**Table 2.** (Continued)

Agent or therapy studied, reference(s)	No. and sex of patients enrolled/ no. analyzed	Design	Regimen (no. of recipients)	Clearance rate (%) at indicated time	
				First assessment at/ after end of treatment	Further assessment(s)
[82]	97	R, PC, DB	Cryo + IFN- $\alpha$ -2b (49) Cryo + PBO (48) Cryo: 3 freeze-thaw cycles 1 $\times$ /w until visibly clear IFN/PBO begun $\leq$ 2 w after last cryo	1 mo: survival for both drugs nearly equal	6 mo: IFN: 31% PBO: 27%
(d) Podophyllin (PD) [59]	60/55 F	O, R	PD 20%: 1 $\times$ /w (27) PDX 0.5%: 2 $\times$ /d, 3 d/w, for 4 w (28)	4 w: PD: 59% (16/27) PDX: 82% (23/28)	3 mo: PD: 48% (13/27) PDX: 71% (20/28)
[54]	252/200 (133 M, 67 F)	O, R	PD 25%: 2 $\times$ /w for 5 w PDX 0.5%: 2 $\times$ /d, 3 d/w, for 5 w	1 w: PD: M: 19% (7/36) F: 19% (5/26) PDX: M: 53% (51/97) F: 37% (15/41)	5 w: PD: M: 72% (26/36) F*: 62% (16/26) PDX: M: 86% (83/97) F*: 78% (32/41)
(e) Bichloroacetic acid (BCA) [28]	83 (80 M, 3 F)	Case series; convenience sample, medical record review	Excision (20); BCA (10); PD (5); IFN- $\alpha$ (5); excision + autogenous vaccine (43)		
(f) Trichloroacetic acid (TCA) [81]	86/86	R	Cryo with pledget, 1 $\times$ /w for $\leq$ 6 w (53) TCA 95%: 1 $\times$ /w for $\leq$ 6 w (33)	$\leq$ 6 w: Cryo: 70% (37/53) TCA: 64% (21/33)	3 mo: Cryo: 86% (37/43) TCA: 70% (21/30)
(g) Electrocautery/electrotherapy [24]	28 F	Case series	Loop electrosurgical excision procedure (LEEP) vs. laser	3 w (evaluation of circumferential rings around lesion): LEEP: 4/28: HPV DNA, $\leq$ 20 mm; no HPV DNA detected beyond 20 mm Laser: 7/28: HPV DNA, $\leq$ 20 mm; 3/28: HPV DNA, $\leq$ 25 mm; 2/ 28: HPV DNA, $\leq$ 35 mm; 0/28: HPV DNA, $\geq$ 40 mm	

**Table 2.** (Continued)

Recurrence rate	Adverse experience(s)	Other
<p>Before 8-w f/u: IFN: 28% (10/36) PBO: 43% (16/37)</p> <p>Before 6-mo f/u: IFN: 69% (25/36) PBO: 73% (27/31)</p>	<p>“Adverse drug reactions noted in 43 (88%) of 49 IFN recipients and in 20 (42%) of 48 PBO recipients.” <i>Resulting in withdrawal of therapy</i>—systemic: influenza-like syndrome (fever, chills, headache, myalgia, nausea; IFN = 3, PBO = 1), bronchospasm (IFN = 1), depression (IFN = 1); Local: injection site reaction (IFN = 6, PBO = 1)</p>	<p>Randomization was within groups based on disease duration; mean no. of warts per patient: IFN = 6.8 and PBO = 7.8; median volume of warts: IFN = 135 mm<sup>2</sup> and PBO = 215 mm<sup>2</sup>; median no. of cryo tx: 3/3 for IFN/PBO groups (no. with ≥6 cryo tx: 12/14, respectively); 97 verified as positive for HPV-6 or -11; no. lost to f/u: IFN = 13 and PBO = 11</p>
<p>3 mo: PD: 19% (3/13) PDX: 13% (3/23)</p> <p>13 w: PD: M: 50% (5/10) F: 43% (3/7) PDX: M: 18% (7/37) F: 24% (5/21)</p>	<p>Local (PD/PDX): tenderness (20/18), burning (19/22), pain (17/18), erythema/erosion (1/7)</p> <p>Local: tenderness, burning, or pain; erythema; edema; erosions (highest incidence occurred at 1 w)</p>	<p>An inclusion criterion was wart size of &lt;5 mm</p> <p>Study protocol initially divided PDX group into 2 study groups, which collapsed into 1 group for analysis; many lost to f/u at 13 w</p>
<p>Excision alone, 50 (10/20); BCA, 50 (5/10); PD, 85 (4/5); IFN-<math>\alpha</math>, 85 (4/5); excision/vaccine, 5 (2/43)</p>	<p>Minor local reactions; details unspecified for vaccine group reactions at the injection site</p> <p>No information</p>	<p>Anal or perianal condyloma; 79 men reported being anoreceptive sex partners; treatment determined by patients' willingness to undergo prolonged vaccine protocol; f/u every w for 12 w, then every mo for 6 mo, then every y for duration of f/u (range, 3 mo to 7 y); patients who had a recurrence were placed on the vaccination protocol, and only 2% of them had further recurrences; no loss to f/u among the excision/vaccine group</p> <p>Newly diagnosed EGWs</p>
<p>LEEP: 14% (4/28) Laser: 4% (1/28)</p>	<p>None referenced</p>	<p>Papillary condylomatous lesions of the vulva on acetowhite test and colposcopy, but no other vaginal or diagnostic lesions found; patient served as own control; indicated LEEP may be more effective in eradicating HPV from surrounding tissues after treatment</p>

NOTE. BCA = bichloroacetic acid; bx = biopsy; Comp = comparative; cryo = cryotherapy; DB = double-blind; EGWs = extragenital warts; epi = epinephrine; f/u = follow-up; 5-FU = 5-fluorouracil; HPMPC = cidofovir; HPV = human papillomavirus; IFN = interferon; O = open; PBO = placebo; PC = placebo-controlled; PD = podophyllin; PDX = podofilox; R = randomized; Sol = solution; TCA = trichloroacetic acid; tx = treatment(s); VC = vehicle-controlled.

\* Data for 5-w assessment not reported; “clearance of all warts at some time during the treatment period.”

Table 2. (Continued)

Agent or therapy studied, reference(s)	No. and sex of patients enrolled/ no. analyzed	Design	Regimen (no. of recipients)	Clearance rate (%) at indicated time	
				First assessment at/ after end of treatment	Further assessment(s)
(h) Laser therapy [97]	146/135 (45 M, 101 F)	R, PC, DB, multicenter	IFN-2- $\alpha$ : 3MU 3 $\times$ /w for 4 w, sc (beginning immediately after laser tx) + laser tx (74) PBO: 3 $\times$ /w for 4 w, sc (beginning immediately after laser tx) + laser tx (72) Laser: 350–750 W/cm <sup>2</sup> , continuous or superpulse	<36 w: IFN: 31% (23/74) PBO: 33% (24/72)	36 w: IFN: 32% (23/71) PBO: 38% (24/64)
[98]	34 M	Case series	CO <sub>2</sub> laser: 3.8 W, continuous, + IFN- $\alpha$ -2b, 10MU intralesionally (14) CO <sub>2</sub> laser: 3.8 W, continuous (20)	Laser/IFN: 1 tx, 79% (11/14) Laser only: 1 tx, 55% (11/20)	
(i) Intralesional IFN [98]	34 M	Case series	CO <sub>2</sub> laser: 3.8 W, continuous, + IFN- $\alpha$ -2b, 10MU intralesionally (14) CO <sub>2</sub> laser: 3.8 W, continuous (20)	Laser/IFN: 1 tx, 79% (11/14) Laser only: 1 tx, 55% (11/20)	
[109]	189/156	DB, R, PC, multicenter	IFN- $\alpha$ -n3: mean dose, 0.92MU/tx; 2 $\times$ /w for $\leq$ 8 w (104) PBO: buffered saline + albumin 2 $\times$ /w for $\leq$ 8 w (85)	1–8 w: IFN: 26% (21/81) PBO: 7% (5/75)	9–11 w: IFN: 37% (30/81) PBO: 15% (11/75) 12–14 w: IFN: 46% (37/81) PBO: 17% (13/75) 15–17 w: IFN: 51% (41/81) PBO: 19% (14/75) 20 w: IFN: 59% (44/81) PBO: 20% (15/75)
[26]	25 (24 M, 1 F)	R, DB, PC; patient as own control	Intralesional tx: (1) <i>r</i> -hIFN- <i>B</i> : 0.033 MU/d, 3 $\times$ /w, for 19 d (2) <i>r</i> -hIFN- <i>B</i> : 1 MU/d, 3 $\times$ / w, for 19 d (3) PBO: 3 $\times$ /w for 19 d	22 d: (1) <i>r</i> -hIFN- <i>B</i> : 38% (9/24) (2) <i>r</i> -hIFN- <i>B</i> : 63% (15/24) (3) PBO: 21% (5/24)	60 d: (1) <i>r</i> -hIFN- <i>B</i> : 48% (11/ 23) (2) <i>r</i> -hIFN- <i>B</i> : 39% (9/ 23) (3) PBO: 13% (3/24)
(j) 5-FU, injectable [111]	Study 1, 132	R, DB, PC, multicenter	5-FU: 30 mg/mL + epi gel (0.1 mg/mL) intralesionally (30 mm <sup>2</sup> / 0.2 mL minimum; >3 mL/w maximum), for $\leq$ 6 tx/8 w Saline substituted for component excluded in test, intralesional, for $\leq$ 6 tx/8 w	5-FU/epi gel: 55% (11/20) 5-FU/epi sol: 41% (9/ 22) 5-FU gel: 36% (8/22) 5-FU sol: 13% (3/24)	3 mo: 5-FU/epi gel, 30% (6/20)

**Table 2.** (Continued)

Recurrence rate	Adverse experience(s)	Other
36 w, proportion with warts: IFN: 68% (48/71) PBO: 63% (40/64)	Systemic (IFN%/PBO%): flu-like symptoms (28/7), headache (31/24), fatigue (12/7), myalgia (12/4), chills (4/4); laboratory (IFN, no./PBO, no.): leukocytopenia (12/0), elevated aspartate aminotransferase level (2/3)	HPV findings from a representative bx sample: negative for HPV = 17% (22/128), HPV-6 = 57% (73/128), HPV-11 = 26% (33/128); Some discrepancy between % listed herein and those in tables in article (efficacy and recurrence % are recomputed from raw data presented in paper; <36 w includes those lost to f/u; 36-w data do not include those lost to f/u); no. of warts: ≤10 = 41%; >10 = 32%; and too numerous to count = 26%; there were no partial responders, by definition
Laser/IFN: 21% (3/14) Laser only: 45% (9/20)	Systemic: with laser/IFN, fever and malaise (6) but no dysuria or urinary retention; (1) postoperative pain; complete healing in 6 w	Mean f/u period: laser, 11.5 mo; IFN, 9.5 mo
Laser/IFN: 21% (3/14) Laser only: 45% (9/20)	Systemic: with laser/IFN, fever and malaise (6) but no dysuria or urinary retention; (1) postoperative pain; complete healing in 6 w	Mean f/u period: laser, 11.5 mo; IFN, 9.5 mo
48 w: IFN: 24% (10/41) PBO: 21% (3/14)	Systemic (IFN, %/PBO, %): myalgias (45/15), fever (40/19), headache (31/15), chills (14/2), fatigue (14/6), malaise (9/9), dizziness (9/4), arthralgia (5/1), back pain (4/1), nausea (4/7), vomiting (3/0), dyspepsia (3/1); local (IFN, %/PBO, %): pain at injection site (5/12), or other, not specified (7/18); laboratory: with IFN, total leukocyte count and granulocyte count decreased and hemoglobin decreased	Anecdotal differences in patients with prior treatment vs. no prior treatment were observed; no prior tx: IFN, 60% (6/10), PBO, 38% (3/8)
60 d: (1) r-hIFN-B: unstated (2) r-hIFN-B: 19% (4/21) of complete response (3) PBO: 54% (13/24)	Treatment was well tolerated; the most common adverse events were flu-like symptoms, in general transient and mild	Mean duration of disease at onset = 482 d; eligibility criteria: colposcopically evident condylomata acuminata (vaginal, vulval, or perianal in F and penile in M); lesions selected for tx were <3 mm in diameter, of similar size, ≤1 cm <sup>2</sup> , separated by ≥1 cm (none in anal canal/urethra)
3 mo: 5-FU/epi gel, 45% (5/11)	Local: mild/moderate cutaneous reactions, resolved by 1 mo; injection site pain	New, recurrent, refractory EGWs of ≥3 mo duration; subjects included if HIV-negative

NOTE. BCA = bichloroacetic acid; bx = biopsy; Comp = comparative; cryo = cryotherapy; DB = double-blind; EGWs = extragenital warts; epi = epinephrine; f/u = follow-up; 5-FU = 5-fluorouracil; HPMPC = cidofovir; HPV = human papillomavirus; IFN = interferon; O = open; PBO = placebo; PC = placebo-controlled; PD = podophyllin; PDX = podofilox; R = randomized; Sol = solution; TCA = trichloroacetic acid; tx = treatment(s); VC = vehicle-controlled.

\* Data for 5-w assessment not reported; "clearance of all warts at some time during the treatment period."

**Table 2.** (Continued)

Agent or therapy studied, reference(s)	No. and sex of patients enrolled/ no. analyzed	Design	Regimen (no. of recipients)	Clearance rate (%) at indicated time	
				First assessment at/ after end of treatment	Further assessment(s)
	Study 2, 187	R, DB, PC	5-FU: 30 mg/mL + epi gel (0.1 mg/mL) intralesionally (30 mm <sup>2</sup> /0.25 mL minimum; >5 mL/w maximum; maximum dose, 900 mg/6 tx) for ≤6 tx/8 w	5-FU/epi gel: 65% (51/78) 5-FU gel: 54% (41/76) PBO gel: 15% (5/33)	
[110]	401	R, DB, PC, phase III	5-FU/epi gel: 6×/w for 8 w (176) 5-FU gel: 6×/w for 8 w (180) PBO: 6×/w for 8 w (45)	After tx: 5-FU/epi gel: 61% (96/158) 5-FU gel: 43% (69/160) PBO: 5% (2/41)	
(k) HPMPC (Cidofovir): (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine [113]	3 (2 M, 1 F)	Case series	HPMPC: 2.5 mg/mL intralesionally (q.o.w.)	After tx series: 100% (3/3)	
[114]	49/46	Phase I/II, O	HPMPC, topical: 0.3%: 1×/d for 5 d, ≤3 cycles 0.3%: 1×/d for 10 d, ≤3 cycles 1%: 1×/d for 5 d, ≤3 cycles 1%: 1×/d for 10 d, ≤3 cycles 3%: 1×/d for 5 d, ≤3 cycles 3%: 1×/d for 10 d, ≤3 cycles	0.3%: 5 d: 0% (0/5) 10 d: 22% (2/9) 1%: 5 d: 9% (1/11) 10 d: 33% (3/9) 3%: 5 d: 0% (0/9) 10 d: 33% (3/9) Overall: 15% (7/46)	

lesions, the duration of disease, and the laser technique employed [14, 15, 47, 52, 61, 92, 97–102].

Studies show that between 3% and 77% of patients treated with laser therapy alone have recurrent EGWs and that patients who receive adjunct therapy in addition to laser ablation have recurrences at similar rates (table 2h) [14, 15, 47, 52, 61, 92, 97–103]. Laser ablation requires specialized training and equipment and consequently is generally reserved for extensive disease. Reported side effects associated with this therapy include scar formation, postoperative pain, vaginal discharge, vulvar swelling, bleeding from the laser bed, dyspareunia, and pseudohyperpyrexia [14, 15, 47, 52, 61, 92, 97–103].

*Interferon.* Interferon is an antiviral, immunomodulatory agent that has been extensively evaluated in vehicle-controlled clinical trials using three modes of administration: intralesional injection, systemic administration, and topical applications. Though intralesional administration has been shown to be effective, systemic and topical administrations have not. Interferon therapy is not routinely recommended because of its cost and the high frequency of systemic adverse side effects.

Side effects are many and include a flu-like syndrome of headaches, chills and fever, and myalgias, as well as impaired concentration, nausea and vomiting, fatigue and malaise, dizziness, back pain, dyspepsia, leukocytopenia, thrombocytopenia,

**Table 2.** (Continued)

Recurrence rate	Adverse experience(s)	Other
	Local: mild to moderate burning, stinging, or transient pain ( $\leq 20$ min) after injections; 5-FU group: erythema, swelling, desquamation, eschar, hyperpigmentation (resolved in $\leq 90$ d); erosion and ulceration associated with complete response to treatment; progressive ulceration (1); severe pain, moderate induration, swelling (1); persistent nodule (1); scarring (6)	
3 mo: 5-FU/epi gel: 50% 5-FU gel: 58%	Local (% of 5-FU-epi gel/5-FU gel/PBO recipients): immediate pain at injection site (96/98/96), erythema (86/83/47), desquamation (58/51/18), swelling (84/80/49), eschar (60/55/7), erosion (72/61/91), ulceration (48/39/0), necrosis (28/21/2), skin discoloration (51/48/7)	Randomization stratified by lesion area; lesions of questionable appearance were biopsied; gel dosing: 0.25 mL/lesion, with total daily dose of 150 mg
12 mo: 0% (0/3)	None noted	HIV-infected/AIDS patients; Bowenoid papulosis (1 M); recurrent exophytic perigenital and intra-anal condylomata (1 M); Bowen's disease and condylomata (1 F), not clear when efficacy was determined on the basis of the abstract in the conference proceedings
Not available	Systemic: none; local: mild to moderate dose-related application-site reactions (19), reversible grade III application-site reactions (4)	

NOTE. BCA = bichloroacetic acid; bx = biopsy; Comp = comparative; cryo = cryotherapy; DB = double-blind; EGWs = extragenital warts; epi = epinephrine; f/u = follow-up; 5-FU = 5-fluorouracil; HPMPc = cidofovir; HPV = human papillomavirus; IFN = interferon; O = open; PBO = placebo; PC = placebo-controlled; PD = podophyllin; PDX = podofilox; R = randomized; Sol = solution; TCA = trichloroacetic acid; tx = treatment(s); VC = vehicle-controlled.

\* Data for 5-w assessment not reported; "clearance of all warts at some time during the treatment period."

and an elevated aspartate aminotransferase level [26, 48, 89–91, 98, 104–108]. The frequency and severity of side effects are significant and may limit the frequency of administration. Furthermore, interferon use is not recommended for patients with hypersensitivity to product ingredients or when interferon-specific neutralizing antibodies are present.

Injection of interferon intralesionally allows precise, localized administration to the affected tissue. Randomized, placebo-controlled, multicenter safety and efficacy studies as well as descriptive case-series studies have evaluated intralesional administration of interferon as both primary and adjunctive therapy and have shown that 42%–62% of patients have complete clearance within 12–20 weeks of injection (table 2i). In

addition, there is no indication that intralesional administration of interferon, used as an adjunctive therapy, is more effective than intralesional administration alone.

Recurrences have been reported to occur in 19%–53% of subjects, though most study reports give rates of 20%–30%, and one study that tested podophyllin with and without administration of intralesional interferon showed a high and nearly equal rate of recurrence in both groups (table 2i) [26, 48, 89, 90, 91, 98, 104–109]. In addition to the systemic side effects noted above, localized pain at the injection site, burning, itching, irritation, pain, and occasional local bleeding have been reported (table 2i) [26, 48, 89, 90, 91, 98, 104–109].

### Treatments in Development

*5-Fluorouracil (5-FU)/epinephrine/bovine collagen gel implant.* 5-FU/epinephrine collagen gel implants combine the antimetabolite 5-FU with a drug delivery system consisting of a vasoconstrictor (epinephrine) and a biodegradable stabilizing gel (bovine collagen). The preparation is injected directly below the wart. Randomized, placebo-controlled studies have been performed and show that warts totally clear in 55%–65% of patients and that as few as 30%–45% have recurrences within 3 months after treatment (table 2j) [110–112].

Hypersensitivity to any product constituents contraindicates use of this preparation, and because 5-FU is a mutagen and teratogen, its use is not recommended for pregnant or lactating women. Like topical 5-FU, use of this treatment requires that female patients effectively use contraception while being treated. Reported adverse reactions among patients treated with 5-FU/epinephrine/collagen implants include desquamation, epithelial erosion, erythema, eschar, hyperpigmentation, and local irritation; mild to moderate burning, stinging, and transient pain at the injection site; and scarring and swelling (table 2j) [110–112]. The required frequent visits, route of administration, and lack of superior efficacy make it difficult to justify its routine use.

*Cidofovir.* Cidofovir (HPMPC:[S]-1-[3-hydroxy-2-phosphonylmethoxypropyl]cytosine) is a newly developed acyclic nucleoside phosphate analogue with broad-spectrum antiviral activity against DNA viruses and is being investigated for treatment of EGWs (table 2k) [113]. Phase II clinical trials in a sample of HIV-infected patients are under review at this time, but preliminary data suggest that between 22% and 33% of patients have wart clearance within 10 days of treatment [114]. Little is known about recurrences after treatment with this agent, and it is contraindicated for patients with known hypersensitivities to any product ingredients. Mild to moderate application-site reactions are the only adverse side effects that have been reported (table 2k).

### Other Treatments

*Systemically administered interferon.* Systemically administered interferon has been extensively and systematically evaluated in the clinical setting with use of randomized, placebo-controlled, multicenter safety and efficacy study designs, and some have investigated the use of systemically administered interferon as an adjunct to other conventional interventions [17, 20, 25, 27, 42, 48, 50, 97, 101, 102, 115–122]. Systemic administration of interferon has been used as a primary and adjunct therapy. Randomized, placebo-controlled studies have shown that as few as zero and as many as 50% of patients treated will have complete clearance of their warts within 4–36 weeks of injection, and there is little indication that adjuvant administration of systemic interferon enhances conventional therapy [17, 20, 25, 27, 42, 48, 50, 97, 101, 102, 115–122]. Between 9% and 68% of patients treated with systemically administered interferon had recurrences in randomized pla-

cebo-controlled studies [17, 20, 25, 27, 42, 48, 50, 97, 101, 102, 115–122].

*5-FU cream and solution preparations.* Topical, patient-applied 5-FU is an antimetabolite that has not undergone rigorous randomized or placebo-controlled studies for the treatment of EGWs. 5-FU has been descriptively evaluated in small human samples, with clearance rates between 10% and 43% [123–126]. One-percent solutions and 5% cream preparations have been used to treat EGWs, and when the two vehicles were compared in a small case series, no statistically significant difference could be detected [123]. Little is known about recurrence of EGWs among patients treated with 5-FU cream, though one study suggests as few as 10% may develop lesions within 6–9 months following successful treatment [126]. Treatment with 5-FU cream is contraindicated for patients with known hypersensitivity to any product ingredients and—because 5-FU is a teratogen and mutagen—for pregnant or lactating women. In addition, the teratogenic characteristics of this treatment require that female patients effectively use contraception while being treated. Adverse side effects of dysuria, epithelial and urinary meatal erosion, erythema, eschar, hyperpigmentation, local irritation, burning, and itching have been reported [123, 125, 126]. Because efficacy is unproven and the risk of toxicity and teratogenicity exists, patient-applied 5-FU cream is not recommended for treatment of EGWs.

### Combined Therapies

Because available treatments have some shortcomings, some clinicians may use combination therapy. There is no evidence to endorse this practice, and more research is required before multimodality treatment recommendations can be formulated. There is reason to believe that combining ablative modalities for a single wart may increase complications without enhancing efficacy.

### Follow-Up Visits

After a patient has been treated for EGWs, follow-up is not mandatory but may serve several functions, especially for patients using patient-applied therapies who have limited provider contact. It is not clear how reliably patients can diagnose EGWs and detect recurrences. A follow-up visit might serve as a means of confirming a wart-free state. In addition, STDs may be major emotional events for patients, and a follow-up visit can provide the opportunity to address the psychosocial issues and provide counseling about general STD prevention strategies.

### Sex Partners

Sex partners of patients with EGWs may also have EGWs and other STDs. Since self- or partner-examination has not been demonstrated to be a reliable diagnostic method for establishing the presence or absence of genital warts, examination

of sex partners may have several benefits. These would include establishing the presence or absence of EGWs and evaluation for other STDs. In addition, counseling about the implications of having a partner with genital warts and about general STD prevention strategies is important. It is not known how to prevent HPV transmission. There is no reason to believe that treating partners will prevent recurrences or otherwise facilitate the treatment of the index case. All women, including the female sex partners of patients with genital warts, should be reminded that cytological screening for cervical cancer is recommended for all sexually active women. Whether or not there is a comparable potential benefit to examining sex partners of women with HPV-related cervical disease is not known at this time.

### HPV and Anal Cancer Screening

High-risk HPV types may be the etiologic agents of anal cancer. Patients with high-risk HPV anal infection can develop high-grade squamous intraepithelial lesions (SILs). At present it is not known how to screen most effectively for anal SILs. Furthermore, the limited amount of data on the risk of anal cancer in those with anal SILs makes it difficult to determine the circumstances in which treatment will be beneficial. Thus, patients who have a history of anoreceptive intercourse, especially those who have anal warts or who have partners with EGWs, should be counseled about the risk of anal cancer. Routine anal cancer screening is not currently recommended.

### Special Considerations

*Pregnancy.* Imiquimod, interferon, podophyllin, and podofilox should not be used during pregnancy. Because genital warts can proliferate and become friable during pregnancy, many experts advocate their removal during pregnancy to prevent an obstetrical complication. Although rare, low-risk HPV types (e.g., HPV 6 or 11) can cause laryngeal papillomatosis in infants and children, and the route of transmission (transplacental, perinatal, or postnatal) is not completely understood. The value of cesarean section in preventing this condition is unknown, and the procedure should not be performed solely in hope of preventing transmission of HPV infection to the newborn. In rare instances, cesarean section delivery may be indicated for women with genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding.

*Immunosuppressed patients.* Persons who are immunosuppressed from HIV infection or other conditions may not respond as well as immunocompetent persons to therapy for genital warts and may have more frequent recurrences after treatment. Squamous cell carcinomas arising in or resembling genital warts may more commonly occur in this population, more frequently requiring biopsy for confirmation and diagnosis.

### Discussion

Despite major limitations in our understanding of genital HPV infection, most patients with EGWs can be rendered wart-free eventually. This process could be simplified if the factors that influence treatment selection were better characterized. There is also a need for trials comparing available treatments in terms of clearance rates, recurrence rates, side effects, and complications of therapy. In addition to these traditional parameters, the general cost-benefit of treatment as well as the cost-benefit of specific therapies need to be established. Discussion of cost was avoided in this review because of the lack of meaningful prospective data in this area.

In addition to treatment of the physical manifestations of genital HPV infections, clinicians need to be trained and prepared to deal with a variety of psychosocial issues that, if not properly addressed, have the potential for causing emotional morbidity that is greater than the physical morbidity due to the warts. These issues should be addressed and information about HPV and EGWs should be presented to the patient both verbally and in the form of written educational materials. As discussed above, it may be useful to evaluate the sex partners of patients with EGWs, both to detect and treat EGWs and other STDs as well as to provide education and counseling about HPV and STDs in general.

Of the traditional STD treatment goals, only one cannot currently be addressed: interruption of transmission through eradication of infection. We do not know when a patient with EGWs is infectious, and elimination of EGWs may or may not influence infectivity. In addition, the long incubation period and the existence of infection and infectivity in the absence of symptoms make interruption of transmission challenging. The greatest hope in preventing transmission would be a prophylactic vaccine.

Treatment can usually eliminate the physical symptoms of EGWs. However, without educational and emotional counseling, the psychosocial symptoms can persist long after the warts have gone. The only well-characterized associated morbidity and long-term sequelae of EGWs are the psychosocial impact and scarring from treatment. Sexually active women with or without EGWs are at risk for developing cervical cancer. However, cervical cancer (and likely anal cancer) are sequelae of high-risk HPV infection and rarely a complication of EGWs or low-risk HPV infection. Most of the morbidity and mortality associated with high-risk HPV infection can be prevented by cervical cancer screening and, perhaps in the future, anal cancer screening.

A comprehensive approach including treatment, counseling, and Pap smear screening is required to effectively care for patients with EGWs. While the gaps in our HPV knowledge are wide, our current knowledge of EGWs enables their effective management.

### References

1. Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. *Epidemiol Rev* 1988; 10:122-63.

2. de Villiers EM. Human pathogenic papillomavirus types: an update. *Curr Top Microbiol Immunol* **1994**;186:1–12.
3. Delius H, Hofmann B. Primer-directed sequencing of human papillomavirus types. *Curr Top Microbiol Immunol* **1994**;186:13–31.
4. IARC Working Group on Evaluation of Carcinogenic Risks to Humans. IARC monographs on the evaluation of carcinogenic risks to humans: human papillomaviruses. Vol. 64. Human papillomaviruses: views and expert opinions of an IARC working group on the evaluation of carcinogenic risks to humans, which met in Lyon, 6–13 June 1995. Lyon, France: World Health Organization, International Agency for Research on Cancer, 1995.
5. Gross G, Pfister H, Hagedorn M, Gissmann L. Correlation between human papillomavirus (HPV) type and histology of warts. *J Invest Dermatol* **1982**;78:160–4.
6. Koutsky LA, Holmes KK, Critchlow CW, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med* **1992**;327:1272–8.
7. Boshart M, Gissmann L, Ikenberg H, Kleinheinz A, Scheurlen W, zur Hausen H. A new type of papillomavirus DNA: its presence in genital cancer biopsies and in cell lines derived from cervical cancer. *EMBO J* **1984**;3:1151–7.
8. Gissmann L. Human papillomavirus DNA in genital tumours. *IARC Sci Publ* **1984**;63:405–11.
9. Munoz N, Bosch F, Shaw KV, et al. The epidemiology of human papillomavirus and cervical cancer. Lyon, France: International Agency for Research on Cancer, **1992**:3–23.
10. Bosch FX, Manos MM, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International Biological Study on Cervical Cancer (IBSCC) Study Group [see comments]. *J Natl Cancer Inst* **1995**;87:796–802.
11. Buschke A, Lowenstein L. Uber carcinomahnliche condylomata acuminata. *Klin Wochenschr* **1925**;4:1726.
12. Boshart M, zur Hausen H. Human papillomaviruses in Buschke-Lowenstein tumors: physical state of the DNA and identification of a tandem duplication in the noncoding region of a human papillomavirus 6 subtype. *J Virol* **1986**;58:963–6.
13. Handley JM, Horner T, Maw RD, Lawther H, Dinsmore WW. Subcutaneous interferon alpha 2a combined with cryotherapy vs cryotherapy. *J Infect Dis* **1993**;167:824–9.
14. Bellina JH. The use of the carbon dioxide laser in the management of condyloma acuminatum with eight-year follow-up. *Am J Obstet Gynecol* **1983**;147:375–8.
15. Ferenczy A. Laser therapy of genital condylomata acuminata. *Obstet Gynecol* **1984**;63:703–7.
16. Syed TA, Khayyami M, Kriz D, et al. Management of genital warts in women with human leukocyte interferon-alpha vs. podophyllotoxin in cream: a placebo-controlled, double-blind, comparative study. *J Mol Med* **1995**;73:255–8.
17. Armstrong DK, Maw RD, Dinsmore WW, et al. Combined therapy trial with interferon alpha-2a and ablative therapy in the treatment of anogenital warts. *Genitourin Med* **1996**;72:103–7.
18. von Krogh G, Szpak E, Andersson M, Bergelin I. Self-treatment using 0.25%–0.50% podophyllotoxin-ethanol solutions against penile condylomata acuminata: a placebo-controlled comparative study. *Genitourin Med* **1994**;70:105–9.
19. von Krogh G, Wikstrom A. Efficacy of chemical and/or surgical therapy against condylomata acuminata: a retrospective evaluation. *Int J STD AIDS* **1991**;2:333–8.
20. Kirby PK, Kiviat N, Beckman A, Wells D, Sherwin S, Corey L. Tolerance and efficacy of recombinant human interferon gamma in the treatment of refractory genital warts. *Am J Med* **1988**;85:183–8.
21. Rader JS, Leake JF, Dillon MB, Rosenshein NB. Ultrasonic surgical aspiration in the treatment of vulvar disease [see comments]. *Obstet Gynecol* **1991**;77:573–6.
22. Greenberg MD, Rutledge LH, Reid R, Berman NR, Precop SL, Elswick RK Jr. A double-blind, randomized trial of 0.5% podoflox and placebo for the treatment of genital warts in women. *Obstet Gynecol* **1991**;77:735–9.
23. Jensen SL. Comparison of podophyllin application with simple surgical excision in clearance and recurrence of perianal condylomata acuminata. *Lancet* **1985**;2:1146–8.
24. Schoenfeld A, Ziv E, Levavi H, Samra Z, Ovadia J. Laser versus loop electrosurgical excision in vulvar condyloma for eradication of subclinical reservoir demonstrated by assay for 2'5' oligosynthetase human papillomavirus. *Gynecol Obstet Invest* **1995**;40:46–51.
25. Panici PB, Scambia G, Perrone L, et al. Oral condyloma lesions in patients with extensive genital human papillomavirus infection. *Am J Obstet Gynecol* **1992**;167:451–8.
26. Monsonego J, Cessot G, Ince SE, Galazka AR, Abdul-Ahad AK. Randomised double-blind trial of recombinant interferon-beta for condyloma acuminatum. *Genitourin Med* **1996**;72:111–4.
27. Handley JM, Horner T, Maw RD, Lawther H, Dinsmore WW. Subcutaneous interferon alpha 2a combined with cryotherapy vs cryotherapy alone in the treatment of primary anogenital warts: a randomised observer-blind placebo-controlled study. *Genitourin Med* **1991**;67:297–302.
28. Wiltz OH, Torregrosa M, Wiltz O. Autogenous vaccine: the best therapy for perianal condyloma acuminata? *Dis Colon Rectum* **1995**;38:838–41.
29. Bauer HM, Ting Y, Greer CE, et al. Genital human papillomavirus infection in female university students as determined by a PCR-based method [see comments]. *JAMA* **1991**;265:472–7.
30. Bauer HM, Hildesheim A, Schiffman MH, et al. Determinants of genital human papillomavirus infection in low-risk women in Portland, Oregon. *Sex Transm Dis* **1993**;20:274–8.
31. Ley C, Bauer HM, Reingold A, et al. Determinants of genital human papillomavirus infection in young women. *J Natl Cancer Inst* **1991**;83:997.
32. Schultz RE, Miller JW, MacDonald GR, et al. Clinical and molecular evaluation of acetowhite genital lesions in men. *J Urol* **1990**;143:920–3.
33. Wikstrom A, Hedblad MA, Johansson B, et al. The acetic acid test in evaluation of subclinical genital papillomavirus infection: a comparative study on penoscopy, histopathology, virology and scanning electron microscopy findings. *Genitourin Med* **1992**;68:90–9.
34. Beutner KR, Richwald GA, Wiley DJ, et al. External genital warts: report of the American Medical Association Consensus Conference. *Clin Infect Dis* **1998**: in press.
35. Fitzpatrick J, Gentry R. Nonvenereal diseases of male genitalia. In: Moschella S, Hurley H, eds. *Dermatology*. 3rd ed. Vol. 1. Philadelphia: WB Saunders, **1992**:1013–4.
36. Jakubovic H, Ackerman A. Structure and function of skin: development, morphology, and physiology. In: Moschella S, Hurley HJ, eds. *Dermatology*. 3rd ed. Vol. 1. Philadelphia: WB Saunders, **1992**:64.
37. Gonzalez E. Molluscum contagiosum and other viruses. In: Moschella S, Hurley H, eds. *Dermatology*. 3rd ed. Vol. 1. Philadelphia: WB Saunders, **1992**:1014–5.
38. Koh H, Ghawan J. Tumors of the skin. In: Moschella S, Hurley H, eds. *Dermatology*. 3rd ed. Vol. 1. Philadelphia: WB Saunders, **1992**:1721–808.
39. Gibson L, Perry H. Papulosquamous eruptions and exfoliative dermatitis. In: Moschella S, Hurley HJ, eds. *Dermatology*. 3rd ed. Vol. 1. Philadelphia: WB Saunders, **1992**:629–36.
40. Oriel JD. Sexually transmitted diseases in children: human papillomavirus infection. *Genitourin Med* **1991**;67:394–9.
41. Champion MJ, Greenberg MD, Kazamel TI. Clinical manifestations and natural history of genital human papillomavirus infections. *Obstet Gynecol Clin North Am* **1996**;23:783–809.
42. Armstrong DK, Maw RD, Dinsmore WW, et al. A randomised, double-blind, parallel group study to compare subcutaneous interferon alpha-2a plus podophyllin with placebo plus podophyllin in the treatment of primary condylomata acuminata. *Genitourin Med* **1994**;70:389–93.

43. Gissmann L, zur Hausen H. Partial characterization of viral DNA from human genital warts (*Condylomata acuminata*). *Int J Cancer* **1980**;25:605–9.
44. Gissmann L, deVilliers EM, zur Hausen H. Analysis of human genital warts (*condylomata acuminata*) and other genital tumors for human papillomavirus type 6 DNA. *Int J Cancer* **1982**;29:143–6.
45. Carr G, William DC. Anal warts in a population of gay men in New York City. *Sex Transm Dis* **1977**;4:56–7.
46. Holly EA, Whittemore AS, Aston DA, Ahn DK, Nickoloff BJ, Kristiansen JJ. Anal cancer incidence: genital warts, anal fissure or fistula, hemorrhoids, and smoking. *J Natl Cancer Inst* **1989**;81:1726–31.
47. Baggish MS. Improved laser techniques for the elimination of genital and extragenital warts. *Am J Obstet Gynecol* **1985**;153:545–50.
48. Eron LJ, Judson F, Tucker S, et al. Interferon therapy for condylomata acuminata. *N Engl J Med* **1986**;315:1059–64.
49. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alpha-2a: a multicenter double-blind placebo-controlled clinical trial. *Acta Derm Venereol* **1993**;73:223–6.
50. Condylomata International Collaborative Study Group. A comparison of interferon alfa-2a and podophyllin in the treatment of primary condylomata acuminata. *Genitourin Med* **1991**;67:394–9.
51. Beutner KR, Conant MA, Friedman-Kien AE, et al. Patient-applied podofilox for treatment of genital warts. *Lancet* **1989**;1:831–4.
52. Duus BR, Philipson T, Christensen JD, Lundvall F, Sondergaard J. Refractory condylomata acuminata: a controlled clinical trial of carbon dioxide laser versus conventional surgical treatment. *Genitourin Med* **1985**;61:59–61.
53. Reid R. The management of genital condylomas, intraepithelial neoplasia, and vulvodynia. *Obstet Gynecol Clin North Am* **1996**;23:917–91.
54. Kinghorn GR, McMillan A, Mulcahy F, Drake S, Lacey C, Bingham JS. An open, comparative study of the efficacy of 0.5% podophyllotoxin lotion and 25% podophyllotoxin solution in the treatment of condylomata acuminata in males and females. *Int J STD AIDS*. **1993**;4:194–9.
55. Wade TR, Ackerman AB. The effects of resin of podophyllin on condyloma acuminatum. *Am J Dermatopathol* **1984**;6:109–22.
56. Petersen CS, Weismann K. Quercetin and kaempferol: an argument against the use of podophyllin? *Genitourin Med* **1995**;71:92–3.
57. Edwards A, Atma-Ram A, Thin RN. Podophyllotoxin 0.5% v podophyllin 20% to treat penile warts. *Genitourin Med* **1988**;64:263–5.
58. Gabriel G, Thin RN. Treatment of anogenital warts. Comparison of trichloroacetic acid and podophyllin versus podophyllin alone. *Br J Vener Dis* **1983**;59:124–6.
59. Hellberg D, Svarrer T, Nilsson S, Valentin J. Self-treatment of female external genital warts with 0.5% podophyllotoxin cream (Condyline) vs weekly applications of 20% podophyllin solution. *Int J STD AIDS*. **1995**;6:257–61.
60. Khawaja HT. Podophyllin versus scissor excision in the treatment of perianal condylomata acuminata: a prospective study [see comments]. *Br J Surg* **1989**;76:1067–8.
61. Lassus A, Haukka K, Forsstrom S. Podophyllotoxin for treatment of genital warts in males: a comparison with conventional podophyllin therapy. *Eur J Sex Transm Dis* **1984**;2:31–3.
62. Potkul RK, Lancaster WD, Kurman RJ, Lewandowski G, Weck PK, Delgado G. Vulvar condylomas and squamous vestibular micropapilloma: differences in appearance and response to treatment. *J Reprod Med* **1990**;35:1019–22.
63. Simmons PD. Podophyllin 10% and 25% in the treatment of ano-genital warts: a comparative double-blind study. *Br J Vener Dis* **1981**;57:208–9.
64. Stone KM, Becker TM, Hadgu A, Kraus SJ. Treatment of external genital warts: a randomised clinical trial comparing podophyllin, cryotherapy, and electrodesiccation. *Genitourin Med* **1990**;66:16–9.
65. Petersen CS, Agner T, Ottevanger V, Larsen J, Ravnborg L. A single-blind study of podophyllotoxin cream 0.5% and podophyllotoxin solution 0.5% in male patients with genital warts. *Genitourin Med* **1995**;71:391–2.
66. Strand A, Brinkeborn RM, Siboulet A. Topical treatment of genital warts in men, an open study of podophyllotoxin cream compared with solution. *Genitourin Med* **1995**;71:387–90.
67. Syed TA, Lundin S. Topical treatment of penile condylomata acuminata with podophyllotoxin 0.3% solution, 0.3% cream and 0.15% cream. *Dermatology* **1993**;187:30–3.
68. Syed TA, Lundin S, Ahmad SA. Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of condylomata acuminata in women: a placebo-controlled, double-blind study. *Dermatology* **1994**;189:142–5.
69. Tyring S, Edwards L, Cherry LK, et al. Safety and efficacy of 0.5% podofilox gel in the treatment of anogenital warts. *Arch Dermatol* **1998**;134:33–8.
70. von Krogh G, Hellberg D. Self-treatment using a 0.5% podophyllotoxin cream of external genital condylomata acuminata in women: a placebo-controlled, double-blind study. *Sex Transm Dis* **1992**;19:170–4.
71. Baker DA, Douglas JM, Buntin DM, Micha JP, Beutner KR, Patsner B. Topical podofilox for the treatment of condylomata acuminata in women. *Obstet Gynecol* **1990**;76:656–9.
72. Pickering R. Self-treatment of genital warts using Warticon. *Br J Sex Med* **1989**;August:320–4.
73. von Krogh G. Penile condylomata acuminata: an experimental model for evaluation of topical self-treatment with 0.5–1.0% ethanolic preparations of podophyllotoxin for three days. *Sex Transm Dis* **1981**;8:179–86.
74. von Krogh G. Topical self-treatment of penile warts with 0.5% podophyllotoxin in ethanol for four or five days. *Sex Transm Dis* **1987**;14:135–40.
75. Beutner KR, Spruance SL, Hougham AJ, Fox TL, Owens ML, Douglas JM Jr. Treatment of genital warts with an immune-response modifier (imiquimod). *J Am Acad Dermatol* **1998**;38:230–9.
76. Edwards L, Ferenczy A, Eron L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. *Arch Dermatol* **1998**;134:25–30.
77. Beutner KR, Edwards L, Fox T, Gayoso K, Hougham A, Owens ML. Comparison of the results from two well-controlled clinical trials of topical imiquimod for the treatment of genital/perianal warts. In: Proceedings of a conference of The Society for Investigative Dermatology (Chicago). **1995**.
78. Edwards L, Ferenczy A, Eron L, et al. Multicenter safety and efficacy trial evaluating three times per week application of 1% and 5% topical imiquimod for the treatment of genital/perianal warts. In: Proceedings of the International Society for Antiviral Research, 8th International Conference on Antiviral Research (Santa Fe, New Mexico). **1995**.
79. Trofatter K, Beutner K, Edwards L, et al. Two vehicle controlled clinical trials of topical imiquimod for the treatment of genital/perianal condylomata acuminata. In: Proceedings of 44th Annual Clinical Meeting of the American College of Obstetricians and Gynecologists. **1996**.
80. Spruance S, Kriesel J, Beutner K, et al. Double blind, dose ranging, placebo controlled, multicenter trial of imiquimod cream for the treatment of genital and perianal warts. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1995**.
81. Abdullah AN, Walzman M, Wade A. Treatment of external genital warts comparing cryotherapy (liquid nitrogen) and trichloroacetic acid. *Sex Transm Dis* **1993**;20:344–5.
82. Eron LJ, Alder MB, O'Rourke JM, Rittweger K, DePamphilis J, Pizzuti DJ. Recurrence of condylomata acuminata following cryotherapy is not prevented by systemically administered interferon. *Genitourin Med* **1993**;69:91–3.
83. Balsdon MJ. Cryosurgery of genital warts [letter]. *Br J Vener Dis* **1978**;54:352–3.
84. Bashi SA. Cryotherapy versus podophyllin in the treatment of genital warts. *Int J Dermatol* **1985**;24:535–6.

85. Bergman A, Bhatia NN, Broen EM. Cryotherapy for treatment of genital condylomata during pregnancy. *J Reprod Med* **1984**;29:432–5.
86. Damstra RJ, van Vloten WA. Cryotherapy in the treatment of condylomata acuminata: a controlled study of 64 patients. *J Dermatol Surg Oncol* **1991**;17:273–6.
87. Ghosh AK. Cryosurgery of genital warts in cases in which podophyllin treatment failed or was contraindicated. *Br J Vener Dis* **1977**;53:49–53.
88. Godley MJ, Bradbeer CS, Gellan M, Thin RN. Cryotherapy compared with trichloroacetic acid in treating genital warts. *Genitourin Med* **1987**;63:390–2.
89. Douglas JM Jr, Eron LJ, Judson FN, et al. A randomized trial of combination therapy with intralesional interferon alpha 2b and podophyllin versus podophyllin alone for the therapy of anogenital warts. *J Infect Dis* **1990**;162:52–9.
90. Scott GM, Csonka GW. Effect of injections of small doses of human fibroblast interferon into genital warts: a pilot study. *Br J Vener Dis* **1979**;55:442–5.
91. Reichman RC, Oakes D, Bonnez W, et al. Treatment of condyloma acuminatum with three different interferons administered intralesionally: a double-blind, placebo-controlled trial. *Ann Intern Med* **1988**;108:675–9.
92. Schwartz DB, Greenberg MD, Daoud Y, Reid R. Genital condylomas in pregnancy: use of trichloroacetic acid and laser therapy. *Am J Obstet Gynecol* **1988**;158:1407–16.
93. Simmons PD, Langlet F, Thin RN. Cryotherapy versus electrocautery in the treatment of genital warts. *Br J Vener Dis* **1981**;57:273–4.
94. McMillan A, Scott GR. Outpatient treatment of perianal warts by scissor excision. *Genitourin Med* **1987**;63:114–5.
95. Reid R. Physical and surgical principles of laser surgery in the lower genital tract. *Obstet Gynecol Clin North Am* **1991**;18:429–74.
96. Reid R. Physical and surgical principles governing carbon dioxide laser surgery on the skin. *Dermatol Clin* **1991**;9:297–316.
97. Condylomata International Collaborative Study Group. Randomized placebo-controlled double-blind combined therapy with laser surgery and systemic interferon-alpha 2a in the treatment of anogenital condylomata acuminatum. *J Infect Dis* **1993**;167:824–9.
98. Davis BE, Noble MJ. Initial experience with combined interferon-alpha 2B and carbon dioxide laser for the treatment of condylomata acuminata. *J Urol* **1992**;147:627–9.
99. Bar-Am A, Shilon M, Peyser MR, Ophir J, Brenner S. Treatment of male genital condylomatous lesions by carbon dioxide laser after failure of previous nonlaser methods. *J Am Acad Dermatol* **1991**;24:87–9.
100. Kryger-Baggesen N, Falck Larsen J, Hjortkjaer Pedersen P. CO<sub>2</sub>-laser treatment of condylomata acuminata. *Acta Obstet Gynecol Scand* **1984**;63:341–3.
101. Petersen C, Bjerring P, Larson J, et al. Systemic interferon alpha-2b increases the cure rate in laser treated patients with multiple persistent genital warts: a placebo-controlled study. *Genitourin Med* **1991**;67:99–102.
102. Reid R, Greenberg MD, Pizzuti DJ, Omoto KH, Rutledge LH, Soo W. Superficial laser vulvectomy. V. Surgical debulking is enhanced by adjuvant systemic interferon. *Am J Obstet Gynecol* **1992**;166:815–20.
103. Ferenczy A, Mitao M, Nagai N, Silverstein SJ, Crum CP. Latent papillomavirus and recurring genital warts. *N Engl J Med* **1985**;313:784–8.
104. Boot JM, Blog FB, Stolz E. Intralesional interferon alpha-2b treatment of condylomata acuminata previously resistant to podophyllum resin application. *Genitourin Med* **1989**;65:50–3.
105. Friedman-Kien AE, Eron LJ, Conant M, et al. Natural interferon alpha for treatment of condylomata acuminata. *JAMA* **1988**;259:533–8.
106. Geffen JR, Klein RJ, Friedman-Kien AE. Intralesional administration of large doses of human leukocyte interferon for the treatment of condylomata acuminata. *J Infect Dis* **1984**;150:612–5.
107. Vance JC, Bart BJ, Hansen RC, et al. Intralesional recombinant alpha-2 interferon for the treatment of patients with condyloma acuminatum or verruca plantaris. *Arch Dermatol* **1986**;122:272–7.
108. Welander CE, Homesley HD, Smiles KA, Peets EA. Intralesional interferon alpha-2b for the treatment of genital warts. *Am J Obstet Gynecol* **1990**;162:348–54.
109. Friedman-Kien A. Management of condylomata acuminata with Alferon N injection, interferon alpha-n3 (human leukocyte derived). *Am J Obstet Gynecol* **1995**;172:1359–68.
110. Swinehart JM, Sperling M, Phillips S, et al. Intralesional fluorouracil/epinephrine injectable gel for treatment of condylomata acuminata: a phase 3 clinical study. *Arch Dermatol* **1997**;133:67–73.
111. Swinehart J, Skinner R, McCarty J, et al. Development of intralesional therapy with fluorouracil/adrenaline injectable gel for management of condylomata acuminata: two phase II clinical studies. *Genitourin Med* **1997**;73:481–7.
112. Swinehart J, Willson C, Lu S, Orenberg E, Korey A. Intralesional accusite (fluorouracil/epinephrine) injectable gel (MPI 5003) for treatment of condylomata acuminata: a two-cycle treatment regime. In: Proceedings of a meeting of The American Academy of Dermatology, 30 July–3 August 1994.
113. Snoeck R, Van Ranst M, Andrei G, et al. Treatment of anogenital papillomavirus infections with an acyclic nucleoside phosphonate analogue [letter]. *N Engl J Med* **1995**;333:943–4.
114. Douglas J, Corey L, Conant M, McGuire B, Jaffe H. A phase I/II study of cidofovir topical gel for refractory condyloma acuminatum in patients with HIV infection. In: Proceedings of the 4th Conference on Retroviruses and Opportunistic Infections. Washington, DC: American Society for Microbiology, **1997**.
115. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alpha-2a: a multicenter double-blind placebo-controlled clinical trial. *JAMA* **1991**;265:2684–7.
116. Bonnez W, Oakes D, Bailey-Farchione A, et al. A randomized, double-blind, placebo-controlled trial of systemically administered interferon-alpha, -beta, or -gamma in combination with cryotherapy for the treatment of condyloma acuminatum. *J Infect Dis* **1995**;171:1081–9.
117. Gall SA, Hughes CE, Trofatter K. Interferon for the therapy of condyloma acuminatum. *Am J Obstet Gynecol* **1985**;153:157–63.
118. Gall SA, Constantine L, Koukol D. Therapy of persistent human papillomavirus disease with two different interferon species. *Am J Obstet Gynecol* **1991**;164:130–4.
119. Gross G, Roussaki A, Baur S, Wiegand M, Mescheder A. Systemically administered interferon alpha-2a prevents recurrence of condylomata acuminata following CO<sub>2</sub>-laser ablation. The influence of the cyclic low-dose therapy regimen. Results of a multicentre double-blind placebo-controlled clinical trial [letter]. *Genitourin Med* **1996**;72:71.
120. Olmos L, Vilata J, Rodriguez Pichardo A, Lloret A, Ojeda A, Calderon MD. Double-blind, randomized clinical trial on the effect of interferon-beta in the treatment of condylomata acuminata. *Int J STD AIDS* **1994**;5:182–5.
121. Reichman RC, Micha JP, Weck PK, et al. Interferon alpha-n1 (Wellferon) for refractory genital warts: efficacy and tolerance of low dose systemic therapy. *Antiviral Research* **1988**;10:41–57.
122. Reichman RC, Oakes D, Bonnez W, et al. Treatment of condyloma acuminatum with three different interferon-alpha preparations administered parenterally: a double-blind, placebo-controlled trial. *J Infect Dis* **1990**;162:1270–6.
123. von Krogh G. The beneficial effect of 1% 5-fluorouracil in 70% ethanol on therapeutically refractory condylomas in the preputial cavity. *Sex Transm Dis* **1978**;5:137–40.
124. Haye KR. Treatment of condyloma acuminata with 5 percent 5-fluorouracil (5-FU) cream [letter]. *Br J Vener Dis* **1974**;50:466.
125. Krebs HB. Combination of laser plus 5-fluorouracil for the treatment of extensive genital condylomata acuminata. *Lasers Surg Med* **1988**;8:135–8.
126. Krebs H. Treatment of extensive vulvar condylomata acuminata with topical 5-fluorouracil. *South Med J* **1990**;83:761–4.