



Korean sexually transmitted infection guidelines 2023 revision, guideline update of viral infections: Genital herpes and anogenital warts

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The Korean Association of Urogenital Tract Infection and Inflammation and the Korea Disease Control and Prevention Agency regularly update, revise, and develop new content for the Korean sexually transmitted infection (STI) guidelines. These professional bodies respond to changing epidemiological trends and evolving scientific evidence, and consider advances in laboratory diagnostics and research. The principal recommendations of the 2023 Korean STI guidelines in terms of viral infection follow: 1) If genital herpes recurs more than 4–6 times annually, suppressive therapy with acyclovir 400 mg orally 2 times/day or famciclovir 250 mg orally 2 times/day or valacyclovir 500 mg orally once a day (for patients with <10 episodes/year) or valacyclovir 1 g orally once daily (for patients with ≥10 episodes/year) is recommended to prevent recurrence; 2) molecular human papillomavirus (HPV) testing is not recommended as a routine test for STI status, nor for determination of HPV vaccination status; and 3) patients should inform their current sexual partners about anogenital warts because the types of HPV that cause such warts can be passed to partners. These guidelines will be updated every 5 years and will be revised when new knowledge on STIs becomes available and there is a reasonable need to improve the guidelines. Physicians and other healthcare providers can use the guidelines to assist in the prevention and treatment of STIs.

Keywords: Genital herpes; Herpes simplex virus; Human papillomavirus; Sexually transmitted infections; Warts

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INTRODUCTION

The Korean Association of Urogenital Tract Infection and Inflammation (KAUTII) and the Korea Disease Control and Prevention Agency (KDCA) update, revise, and develop new content for the Korean sexually transmitted infection

(STI) guidelines on an ongoing basis. These professional bodies respond to changing epidemiological trends and evolving scientific evidence, and consider advances in laboratory diagnostics and research. This chapter introduces how the guidelines are developed and the major changes to the guidelines in 2023 for the treatment of viral infections that

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cause genital herpes and anogenital warts.

MATERIALS AND METHODS

The current KAUTII and KDCA guidelines were first published in 2011 (1st edition) and revised in 2016 (2nd edition). The updates of the 2023 version (3rd edition) are based on the former guidelines and the recent literature. The Korea Medical Guideline Information Center (KoMGi) uses the five terms of the United Kingdom National Institute for Health and Clinical Excellence to indicate the extent of guideline revisions: update of the whole guideline; update of part of the guideline; no update; transfer to the static list; and withdrawal of the guideline. The 2023 edition includes an update of part of the guideline, wherein information from foreign guidelines has been adopted/accommodated, or developed, to reflect the Korean context.

We evaluated 10 existing overseas treatment guidelines in terms of their suitabilities for local adaptation. The Korean Appraisal of Guidelines for Research & Evaluation version 2.0 scale of the KoMGi was used to determine the qualities of these guidelines. Two guidelines that rigorously evaluated progress in treatment development and applicability were selected: the 2021 World Health Organization guidelines for the management of symptomatic STIs and the 2021 Centers for Disease Control STI treatment guidelines. Clinical recommendations were developed using the population (or patient), intervention, comparison, outcome (PICO) framework. A modified Delphi method was employed to attain consensus in terms of clinical recommendations. We used the modified grading of recommendations assessment, development, and evaluation (GRADE) system for the assessment. We evaluated and graded evidence, and developed recommendations, as suggested by the British HIV Association; these suggestions have been widely accepted in Europe [1]. The strength of each recommendation was graded 1 or 2, and each recommendation was further subgraded A, B, C, or D depending on the level of evidence, as follows: 1A, strong recommendation with high-quality evidence; 1B, strong recommendation with evidence of moderate quality; 1C, strong recommendation with low-quality evidence; 1D, strong recommendation with very low-quality evidence; 2A, weak recommendation with high-quality evidence; 2B, weak recommendation with evidence of moderate quality; 2C, weak recommendation with low-quality evidence; and 2D, weak recommendation with very low-quality evidence.

The revisions made by the Korean STI Guidelines Revision Committee underwent internal and external reviews. The external societies and institutions participating in the

review were the Korean Urological Association, the Association of Korean Urologists, the Korean Society of Obstetrics and Gynecology, the Korean Association of Obstetricians and Gynecologists, the Korean College of Obstetrics and Gynecology, the Korean Society for Laboratory Medicine, the Korean Society of Clinical Microbiology, the Korean Society of Infectious Diseases, and the KDCA Division for HIV/AIDS Prevention and Control.

RESULTS

1. Genital herpes

1) Epidemiology

Herpes simplex virus (HSV) infection is the most common of all STI-causing genital ulcers. Both HSV-1 and HSV-2 can trigger genital herpes. Most recurrent cases are caused by HSV-2; 11.9% of those aged 14–49 years are infected in the United States [2]. However, an increasing proportion of genital infections have been attributed to HSV-1, especially in young women and men who have sex with men [3,4]. In Asia, over 10% (attaining 12.1%) of general populations are infected with HSV-2, but the seroprevalence has declined over the last three decades. HSV-2 accounts for 48.2% of all genital ulcers and 75.9% of all genital herpes [5]. In a sample of the Korean general public, the seroprevalence of 1,855 subjects aged over 13 years in southern Korea was 20.1% (20.9% for man and 22.4% for woman). The figure for commercial sex workers (81.6%) was about 10-fold higher than that of other woman [6].

2) Clinical features

Both HSV-1 and HSV-2 infections are lifelong. About 80% of all symptomatic patients exhibit typical genital symptoms and signs [7]. The clinical symptoms vary widely, from asymptomatic infection to painful genital sores or blisters. The primary symptom is often small groups of vesicles on the genital mucosa that subsequently rupture to form shallow painful ulcers that may be accompanied by itching, burning, dysuria, and tender enlarged lymph nodes [8]. The classical manifestations are genital, but herpes lesions can also occur around the anus, buttocks, and thighs [9]. Painful vesicles may evolve into erosions or ulcers that secrete infectious fluids and form crusts; such lesions may persist for 2–3 weeks (Fig. 1). Most persons serologically positive for HSV-2 are asymptomatic, but viral shedding may be detected in the genital area [10]. As asymptomatic individuals can unknowingly transmit the virus to sexual partners, an awareness of the various symptoms and an acceptance of the importance of comprehensive testing are important.

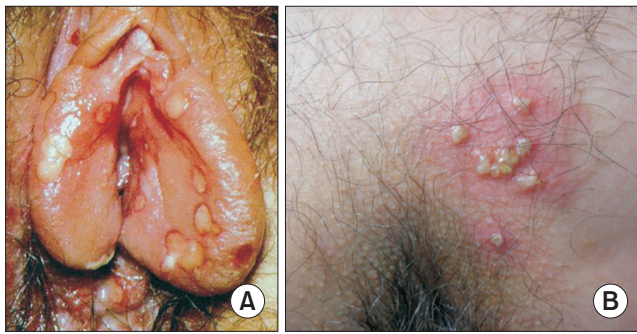


Fig. 1. (A) Painful ulcerative lesion of genital herpes. (B) Localized bul-ous lesion of genital herpes.

3) Diagnosis

Genital herpes may be diagnosed via direct viral detection in genital lesions. HSV DNA detection based on polymerase chain reaction or other nucleic acid amplification technologies is more sensitive and rapid than is viral culture [11]. The latter techniques amplify viral genetic material from clinical samples, sensitively enabling the identification of both symptomatic and asymptomatic infections. Type-specific serological tests are recommended in the absence of lesions, although such tests do not indicate the sites of infection. Serological assays, such as type-specific immunoglobulin G antibody testing, evaluate the immune response to HSV infection [12]. These tests detect antibodies generated in response to HSV exposure and can distinguish recent from past infections [13].

4) Treatments

Treatments should address the chronic nature of the infection rather than focus solely on the present genital lesions. Systemic antiviral drugs are used to treat genital herpes but do not completely eradicate the virus. The goal of such therapy is to reduce the signs and symptoms of infection and prevent the development of new lesions. The available drugs include nucleoside analogs such as acyclovir, valacyclovir, and famciclovir. All are used to treat the first and recurrent clinical episodes, and as suppression therapies, but differ in terms of dosage and the duration of use (Table 1). Topical antiviral therapy is discouraged because no clinical benefit has been demonstrated [14].

Suppression therapy seeks to delay the time to first recurrence after the initial clinical outbreak and to reduce the frequency of recurrences by approximately 70%–85%. Patients on suppressive therapy for recurrent herpes exhibit improvements in the quality-of-life. There is no evidence that long-term suppressive therapy induces antiviral drug-resistance in individuals with normal immune function. In patients with severe HSV infections or disseminated infec-

tions accompanied by complications such as pneumonia, hepatitis, or central nervous system involvement, intravenous acyclovir may be necessary; the recommended dose is 5–10 mg/kg every 8 hours for 2–7 days or until clinical improvement is observed, followed by oral antiviral therapy to a minimum of 10 days of treatment.

HIV-infected individuals tend to experience more severe and chronic herpes infections than do non-HIV-infected individuals [15]. Therefore, HIV patients require higher doses of antiviral drugs for longer durations. Suppressive therapy effectively reduces HSV outbreaks in HIV patients, and is sometimes recommended for a full 6 months [16].

Genital herpes in pregnant women requires careful management given the possibility of vertical fetal transmission and thus neonatal HSV infection [17]. Commencing at 36 weeks of pregnancy, prophylactic suppressive therapy with acyclovir or valacyclovir should be offered to all women with histories of genital herpes. This reduces HSV recurrence by 75% during delivery, decreases the need for cesarean sections caused by recurrent genital herpes by 40%, and lowers viral shedding during delivery [18]. Higher doses of acyclovir or valacyclovir may be required during pregnancy given the increased renal excretion of these drugs [19]. The American Academy of Obstetricians and Gynecologists and the American Academy of Pediatrics recommend cesarean sections for all pregnant women with active HSV genital lesions or who exhibit prodromal symptoms during labor [20].

5) Management of sexual partners

Comprehensive management of sexual partners is multifaceted, and includes diagnosis, education, treatment, and prevention. Disclosure of HSV-2 infection reduces the risk of HSV transmission between partners infected with HSVs that differ in terms of the serotypes [21]. Similarly, disclosure of a genital HSV-1 infection may delay the time to partner HSV-1 acquisition. Accurate and reliable diagnoses of genital herpes in sexual partners are essential. Modern, precise diagnostic methods that evaluate and confirm infection status are crucial. Sexual partners must be given information on how infection happens, the modes of transmission, the symptoms, and the treatment options. It is essential to explain how STIs may be prevented using certain measures during sex. Infected sexual partners require appropriate treatment plans, such as antiviral therapy combined with guidelines on how to adhere to medication, alleviate symptoms, and prevent recurrences.

Table 1. Recommended regimens for genital herpes

Clinical features	Recommended regimens	Comments
First clinical episodes	Valacyclovir 1 g orally 2 times/day for 7–10 days	Treatment may be extended if healing is incomplete after 10 days of therapy.
	Famciclovir 250 mg orally 3 times/day for 7–10 days	
	Acyclovir 400 mg orally 3 times/day for 7–10 days	
Severe episodes	Intravenous acyclovir 5–10 mg/kg every 8 hours for 2–7 days or until clinical resolution is attained, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10–14 days course of total therapy.	
Recurrent episodes	Valacyclovir 500 mg orally 2 times/day for 5 days Famciclovir 125 mg orally 2 times/day for 5 days Acyclovir 400 mg orally 3 times/day for 5 days	
Suppressive therapy	Valacyclovir 500 mg orally once a day	Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years, and with valacyclovir and famciclovir for 1 year.
	Valacyclovir 1 g orally once a day (≥ 10 episodes/year)	
	Famciclovir 250 mg orally 2 times/day Acyclovir 400 mg orally 2 times/day	
HIV-infected patients		
Episodic infection	Valacyclovir 1 g orally 2 times/day for 5–10 days Famciclovir 500 mg orally 2 times/day for 5–10 days Acyclovir 400 mg orally 3 times/day for 5–10 days	
Suppressive therapy	Valacyclovir 500 mg orally 2–3 times/day Famciclovir 500 mg orally 2 times/day Acyclovir 400–800 mg orally 2–3 times/day	
Pregnant women		
Suppressive therapy	Valacyclovir 500 mg orally 2 times/day Acyclovir 400 mg orally 3 times/day	Treatment recommended starting at 36 weeks' gestation.

2. Anogenital warts

1) Epidemiology

Genital warts have an annual incidence of 1%, and are the most common of all STIs; the prevalence has increased by at least four-fold over the last two decades to presently exceed 50%. Before the era of human papillomavirus (HPV) vaccines, approximately 355,000 new anogenital wart cases were reported annually [22]. In Korea, the prevalences in both males and females increased from 2007 to 2015. The number of patients rose by approximately 1.8-fold over the last 9 years [23]. More than 90% of such warts are caused by nononcogenic HPVs of type 6 or 11 [24]; these HPV subtypes have also been associated with conjunctival, nasal, oral, and laryngeal warts.

2) Clinical features

Anogenital warts are usually asymptomatic [25]. However, some patients report itching, burning, or tenderness depending on wart size and location. The warts typically present as papules or plaques on the external genitalia, perianal

skin, perineum, or groin (Fig. 2).

3) Diagnosis

Diagnosis is usually visual but can be confirmed via biopsy, which is indicated if a lesion is atypical (i.e., pigmented, indurated, ulcerated, or fixed to underlying tissue) [26]. The examination should include urethral exploration. Vaginal and cervical warts are found in about 15% and 6% of all female patients with anogenital warts [27]. Initial colposcopy is required when lesions are apparent on the vaginal opening or when cervical or vaginal lesions are suspected. Both sexes should undergo perianal examination at initial evaluation and when lesions are present or anal irritation is reported. Proctoscopy and a digital rectal examination are essential if an intra-anal wart is suspected; such a wart is an external lesion extending into the anus associated with anal bleeding or discharge. The acetic acid test is sometimes used to diagnose asymptomatic HPV lesions, but is not accurate [28]. Certain anogenital lesions (Fordyce spots, pearly penile papules, condyloma lata, molluscum contagiosum, seborrheic kerato-

sis, and the lesions of Paget disease; collectively termed condyloma accuminata) can resemble anogenital warts, but do not respond to wart treatment.

Molecular HPV testing is not recommended; the results are not confirmatory (recommendation grade 1D). Such testing does not reveal HPV vaccination status [26]. An HPV test is one component of the battery of cervical cancer tests and is a recommended follow-up test for women evidencing

abnormal Pap smear results [29].

4) Treatments

Treatments seek to remove the warts and ameliorate any symptoms. Warts trigger considerable psychosocial distress; wart removal relieves cosmetic concerns. Many warts spontaneously resolve in <1 year; some patients may be content to await spontaneous resolution. The available therapies reduce, but probably do not eradicate, HPV infectivity. It remains unclear whether a reduction in the HPV viral DNA load reduces future transmission. The recommended anogenital wart treatments by wart location are listed in Table 2. In pregnant women, podofilox, podophyllin, and sinecatechins should not be used; and imiquimod should be employed with caution. About half of all pregnancy-related genital warts spontaneously regress in the first 3 months after birth. HPV types 6 and 11 may trigger respiratory papillomatosis in infants and children [30]. However, it is unclear whether cesarean section prevents these effects. For women with genital warts, a cesarean section is required only when the pelvic outlet is blocked by the warts or when excessive bleeding is expected during vaginal delivery. Immunocompromised patients are more likely than others to develop anogenital warts, but no specific treatment is yet available. However, bleeding may be more common in patients with squamous cell carcinomas; biopsy is required if this condition



Fig. 2. Condylomata acuminata on the external genitalia.

Table 2. Recommended regimens for anogenital warts according to locations

Clinical features	Recommended regimens	Comments
External anogenital warts	Imiquimod 5% cream Podofilox 0.5% solution or gel Sinecatechins 15% ointment TCA or BCA 80%–90% solution Cryotherapy with liquid nitrogen or cryoprobe Surgical removal by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery	Might weaken condoms and vaginal diaphragms.
Urethral meatus warts	Cryotherapy with liquid nitrogen Surgical removal	
Vaginal or cervical warts	Cryotherapy with liquid nitrogen Surgical removal TCA or BCA 80%–90% solution	The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation. For women who have exophytic cervical warts, a biopsy evaluation to exclude HSIL should be performed before treatment is initiated.
Intra-anal warts	Cryotherapy with liquid nitrogen Surgical removal TCA or BCA 80%–90% solution	

TCA, trichloroacetic acid; BCA, bichloroacetic acid; HSIL, high grade squamous intraepithelial lesion.

is suspected [31].

5) Management of sexual partners

Patients should tell their current sexual partners that they have anogenital warts because the HPV types that cause such warts can be passed to partners (recommendation grade 1D). It is difficult to define recommendations in terms of informing future sex partners because the duration of viral persistence after wart resolution is unknown; there is no evidence that simply telling sexual contacts that one has genital warts reduces the risk of sexual transfer. HPV is transmitted via oral, anal, and vaginal contact, as well as self-inoculation. Heterosexual vaginal intercourse features more woman-to-man than man-to-woman transmission. Patients already infected with one type of HPV may be infected by additional types of HPV. Condoms help to prevent HPV transmission, but condoms may not cover all warts and some warts may not be identified (and thus not covered with condoms). It is impossible to quantify the extent of protection afforded by condom use [26].

CONCLUSIONS

These guidelines will be updated every 5 years and will be revised when new data on STIs are published and it is then reasonable to improve the guidelines. Physicians and other healthcare providers can use the guidelines to prevent and treat STIs.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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