Genital Herpes in Human Immunodeficiency Virus Infected Patients

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Abstract

Genital herpes is a recurrent, lifelong sexual transmitted infection caused by HSV, especially type 2. Genital herpes is the most common infection in HIV patient. HSV-2 can increase the risk of HIV acquisition 2 to 3 times. Clinical manifestations of genital herpes can be different between HIV-infected and non-HIV patients. HIV-infected patients have a high risk of developing chronic and severe genital ulcers with atypical manifestation, prolonged healing, and resistant to treatment, depends on CD4 count. Genital herpes can be diagnosed based on history, clinical manifestation, laboratory and histopathologic examination. Management of genital herpes includes education and counseling patients and sexual partners, systemic antiviral, and symptomatic treatment.

Introduction

Genital herpes is a sexually transmitted infection caused by Herpes Simplex Virus (HSV), recurrent and lifelong.1 There are 2 types of HSV, HSV-1 and HSV-2. Generally, HSV-1 causes the majority of cases of orolabial herpes, while HSV-2 is associated with most cases of genital herpes. However, both can infect the oral and genital areas.2,3 Herpes simplex virus type 2 (HSV-2) is the most common cause of genital ulcers. The clinical manifestations of genital herpes can be seen clearly, but most infections are asymptomatic and can be transmitted through sexual intercourse and vertical from mother to fetus.2,4

Genital herpes is a common sexually transmitted infection worldwide and a risk factor for the acquisition and transmission of the Human Immunodeficiency Virus (HIV).2 The incidence of genital herpes cannot be reported with certainty, but an estimated 500,000 new cases occur each year. According to the World Health Organization (WHO), an estimated 491 million people aged 15-49 years (13%) worldwide were infected with HSV-2 in 2016 and it tends to increase. The highest prevalence occurred in Africa (44% women and 25% men), followed by America (24% women and 12% men). Prevalence also increases with age, with a peak of young adults and more women than men with an estimated 313 million women and 178 million men.5,6

Typical lesions of genital herpes are grouped vesicles with an erythematous base, pustules, and ulcers, accompanied by complaints of pain, itching,

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dysuria, vaginal / urethral discharge, and painful inguinal lymphadenopathy. There may be prodrome symptoms such as fever, headache, malaise and myalgia. The lesions heal within 2-3 weeks. Predilection in men in the glands of the penis and preputium, whereas in women on the vulva, perineum, buttocks, vagina, and cervix. The clinical manifestations of genital herpes can be divided into first episodes (primary and non-primary) and recurrent episodes.1,2

Human Immunodeficiency Virus (HIV) is the cause of Acquired Immune Deficiency Syndrome (AIDS), which is a syndrome with symptoms of opportunistic infections or certain cancers due to a decreased immune system due to HIV infection. HSV-2 infection is the most common infection in HIV patients, accounting for 60-90% of HIV-infected patients. HSV-2 infection increases the risk of HIV acquisition 2 to 3 times.5,6,8 The clinical manifestations of genital herpes patients with or without HIV can be different. Patients with HIV have a high risk of developing chronic and severe genital ulcers with atypical features, prolonged healing, and are easily resistant to treatment. This depends on the CD4 count.4,9,10

**Pathogenesis**

Herpes simplex virus-2 is a double-stranded deoxyribonucleic acid (dsDNA) virus from the Herpesviridae family subfamily α-herpesvirus, is neurotropic, rapidly replicates, and infects various cell types such as epithelial cells, fibroblasts, neurons, and leukocytes.3,9,11 Herpes virus consists of 4 parts, namely the electron-opaque nucleus, theicosahedral capsid around the nucleus, the amorphous tegument containing viral encoded proteins around the capsid, and the outer envelope with glycoprotein spikes on its surface. The capsid is a protein structure surrounded by a tightly attached, tegumentary membrane. The capsid and tegument are surrounded by envelopes containing glycoproteins (gB-gN), lipids, and polyamines. Glycoproteins function as an intermediary for the attachment of viruses to host cells and induce a host immune response against viruses.3,9

The incubation period for HSV ranged from 2-12 days (mean 4 days).12 Transmission of HSV infection occurs through sexual contact with fluids from an HSV infected patient such as semen, saliva or direct contact with the vesicle fluid of herpes lesions.3 The risk of HSV transmission is highest when there are lesions or prodrome symptoms, it can also occur during asymptomatic viral shedding. Fifty to 90% of sexual partners are unaware that they are infected with HSV. Asymptomatic viral shedding occurs most frequently in the first year after the primary episode.9

HSV infection occurs when viral particles enter the skin or mucous membranes through abrasion or microtrauma. The entry of the virus is preceded by the attachment of the virus to the cell surface receptors (heparan sulfate). This fusion results in the viral capsid being transported to the nuclear pore and releasing viral DNA into cells, wherein the prepackaged transactivator of transcription, VP16, residing in the tegument, initiates transcription of a 3 gene cascade. Viral α gene (immediate-early) starts replication and activates β gene (delayed-early). Genes β produce enzymes needed for viral replication such as thymidine kinase HSV and DNA polymerase. The last γ gene expressed codes for structural proteins. The nucleocapsid formation of the herpes virus begins in the nucleus. The nucleocapsid together with the envelope develops through the inner lamellae of the plasma membrane. Envelope particles are transported to the cytoplasm through the plasma membrane by membrane-bound vesicles and the Golgi apparatus. The release of virion progeny takes place in the plasma membrane.9 Then the virus will spread to surrounding cells and damage epithelial cells to form vesicles containing cellular debris, inflammatory cells, and virion progeny. Next, the virus enters the sensory nerve fibers and migrates to the sacral nerve ganglion. In the ganglion of the sacral nerves, the virus causes latent infection where DNA transcription continues but at low levels. These latent infections are lifelong which can undergo periodic reactivation and replication. When reactivation occurs, the virus descends from the nerve ganglion to the skin or genital mucosa. This reactivation process generally causes genital ulcers, but it can also be asymptomatic. Herpes simplex virus
can also spread via lymph vessels to regional lymph nodes.\textsuperscript{13,14} When an infection occurs, the body will activate cellular and humoral immunity to control the spread of infection and HSV replication. CD4 and CD8 lymphocyte T cells, natural killer cells (NK cells), macrophages, and inflammatory cytokines such as interferons-γ are important protective cells against HSV. The cellular immune response is an important factor in determining the severity and recurrence of HSV. The humoral immune response does not prevent recurrences.\textsuperscript{9}

It has long been known that there is a synergistic relationship between HIV and HSV-2. HIV infection has clinical implications and can lead to HSV-2 reactivation. HSV-2 infection increases the risk of HIV infection acquisition and transmission (Figure 1).\textsuperscript{15,16} The high rate of asymptomatic herpes virus shedding results in undiagnosed genital herpes and the continuous spread of HSV-2 and HIV.\textsuperscript{15} There are 3 important mechanisms of HIV transmission in HSV-2 patients, namely:\textsuperscript{12}

1. Symptomatic HSV-2 genital ulcers cause local inflammation and damage to the genital tract mucosa thereby facilitating HIV-1 entry during exposure to HIV-infected genital fluids.
2. HSV-2 genital ulcers selectively increase local recruitment of CD4 T cells that are targeted for mucosal adhesion of HIV-1.
3. Viral replication in HSV-2 lesions.

![Figure 1. Inter-relationships between HSV-2 and HIV infections.\textsuperscript{16}](image)

Some literature describes the mechanism of HSV-2 infection in enhancing HIV acquisition primarily through CD4 cell recruitment and increasing the expression of important HIV receptors at the port of entry.

- HSV-2 infection can increase the concentration of cervical HIV target cells. HSV-2 infection is associated with a 10-fold increase in cervical CD4 T cells expressing CCR5, which is the main target of mucosal HIV infection. Women with HSV-2 also had a higher number of CD4-expressing CD69 T-cells and DC-SIGN-expressing cervical dendritic cells higher in the cervicovaginal mucosa. There is also an influx of
dendritic cells and CD4 and CD8 T cells into recurrent HSV-2 ulcers. These cells, which have the CCR5, CXCR4, and DC-SIGN receptors, persist for several months, despite resolution of the lesion. Langerhans cells prevent HIV transmission through the C-type lectin, langerin, which can degrade the virus thereby reducing transmission of HIV to T cells. Herpes simplex virus-2 can decrease the expression of langerin so that Langerhans cells are more susceptible to HIV infection. This makes it easier for HIV to infect Langerhans cells and T cells. Several other studies have shown that keratinocytes infected with HSV-2 produce human β defensins and LL-37 protein which can increase the expression of HIV receptors in Langerhans cells. The two things previously mentioned prove that HSV-2 not only inhibits Langerin function but also makes it easier for Langerhans cells to become infected with HIV. T cells, the main target of HIV infection, migrate to the genital skin and mucosa under the influence of the chemokine CXCL-9.

The biopsy results containing the inflammatory infiltrate showed that local HIV replication was 3 to 5 times more than in areas without the inflammatory infiltrate. HSV-2 infection decreases mucosal innate immunity and induces a mucosal inflammatory response. HSV-2 infection caused a significant reduction in secretory leukoprotease inhibitor (SLPI) gene expression by human cervical epithelial cells, which persisted despite acyclovir treatment. This suggests that the virus downregulates SLPI as a strategy to avoid the immune system. The SLPI gene can inhibit HIV infection. Decreased SLPI concentrations lead to increased transcription factor κB (NF-κB)-mediated proinflammatory pathways. Herpes simplex virus-2 can also directly activate NF-κB which induces HIV replication. During infection, HSV-2 induces innate and adaptive immune responses in the genital mucosa. Chemokine induction causes recruitment of CD4 T cells and dendritic cells, which are the target of HIV infection. The proinflammatory mediators produced by epithelial cells and immune cells facilitate HIV replication. Herpes simplex virus-2 induces HIV replication directly in HIV-1 long terminal repeat or indirectly through stimulation of the production of TNF-α, interleukin (IL)-6, IL-8, and monocyte chemotactic protein-1 by epithelial cells.

**Clinical manifestations**

The clinical manifestations of HSV are varied and can cause psychological and psychosocial problems. The severity of clinical manifestations and recurrences is influenced by viral and host factors. The clinical manifestations of herpes can be divided into first episodes and recurrent episodes. The first episode was divided into primary, in patients without previous HSV-1 or HSV-2 antibodies, and non-primary, in patients with previous HSV-1 or HSV-2 antibodies. Most HSV infections are asymptomatic. Predilection in men in the glands of the penis and prepuce, whereas in women on the vulva, perineum, buttocks, vagina, and cervix.

**Primary first episode genital herpes**

Primary genital herpes is characterized by local and systemic symptoms that last a long time. The most common local symptoms are pain, dysuria, urethral or vaginal discharge, genital and sacral paresthesias, accompanied by painful inguinal lymphadenopathy. Lesions occur 3-14 days after infection. Systemic symptoms occur early in the course of the disease, after a mean incubation period of 6-8 days, peak 4 days after disease onset and subside slowly in 3-4 days later. The most common systemic symptoms are headache, fever, myalgia, lethargy and photophobia. About 40% of men and 70% of women experience systemic symptoms during the primary episode. Local symptoms of itching, erythema, and pain generally occur within 1-2 days of preceding the lesion. The first lesions appear as small, clustered, painful vesicles or pustules above the erythematous base, break easily and form ulcers within 2-4 days. Widespread lesions can coalesce to form large ulcers. Atypical features such as deep necrotic ulcers may occur. New cluster lesions may appear at week 2.
week 3, crusting begins and the process of re-epithelialization begins. When the lesion is on the mucosa, usually no crusting or scarring occurs. On physical examination, there is an enlarged inguinal and femoral lymphadenopathy that is painful, hard, and does not fluctuate, which occurs at week 2 or 3 and persists even after the lesions have healed.9

About 88% of women with a first-episode genital herpes infection have cervicitis. Urethral discharge and dysuria occur in one-third of men. The urethra was clear and mucoid. HSV pharyngitis can occur with orogenital sexual contact. The duration of time taken from lesion onset to resolution in women was longer (mean 20 days) than men (mean 16.5 days) and the duration of viral shedding (onset of lesions to viral culture still positive in the lesion) was around 12 days.9

Non-primary first episode of genital herpes

About 50% of first-episode HSV-2 genital ulcer patients have HSV-1 antibodies. HSV neutralizing antibodies inactivate extracellular viruses and interfere with the spread of HSV infection. Non-primary first-episode patients had a lower frequency of systemic symptoms, shorter pain duration, fewer lesions, and a shorter duration of healing than primary infections.9

Recurrent genital herpes

At least 90% of infected patients have recurrent HSV-2 genital herpes and 88% of them have at least 1 recurrence within the first 12 months of the episode. Recurrence can be triggered by emotional stress, UV radiation, concomitant infections, and menstruation. Most genital herpes patients can predict recurrence through local prodromal symptoms, such as a mild tingling sensation that occurs about 48 hours before the lesion develops. The risk of viral shedding is high during prodrome symptoms, even when there are no lesions. False prodromes (prodromal symptoms without genital lesions) may occur and are more common in patients who have frequent recurrences. Recurrent genital herpes is the mildest form, with few vesicles arising (about 3-5), in the glans penis or prepuce of men and is usually unilateral. Systemic symptoms experienced 5% of men and 12% of women. Women experience genital ulcer pain more often with a longer duration than men. Peak viral shedding occurred within 48 hours of lesion onset and lasted 4 days. The mean time from onset to crusting is about 5 days. Re-epithelialization occurs in 6-10 days. Occasionally, only itching, erythema and edema are found without vesicles, crusting or ulcers (asymptomatic). In patients with recurrent genital herpes can also be found atypical features. Genital herpes can be misdiagnosed as recurrent vaginitis, urogenital tract infection, or candida infection in women and as folliculitis, condom allergy, or other dermatoses in men.9

Genital herpes in HIV patients

The clinical manifestations of HSV infection in HIV vary depending on the patient’s immune status.17 All clinical manifestations of HSV infection in immunocompetent patients can occur in HIV patients, especially during its early stages. However, as the immune status decreases, the clinical manifestations are often atypical, wider, longer lesion duration, painful, easily resistant to treatment, and often recurrent, especially when the CD4 count is <250 cells / mm3.9,18,19,20 HSV infection in HIV patients also has local and systemic symptoms that last longer and spread the virus longer (more than 30 days), while the recurrence ranges from 0-20 episodes per year. The recurrence frequency increases when the CD4 count is <50 cells / mm3.17 Atypical features may include (1) hyperkeratotic / verucous lesions mimicking condyloma acuminata or carcinoma of the verosa in advanced HIV patients (2) vegetative plaque, expanded, confluent with ulceration with yellow exudate (Figure 2) (3) chronic and persistent ulcers that are very painful and large in size (Figure 3), and (4) generalized papular eruptions in the form of discrete papules or papulovesicles, erosions, and crusts. Lesions may progressively become hemorrhagic and necrotic. Generally, it occurs in patients with CD4 counts less than 100 cells / mm3.21 Perianal herpes is common in patients who have sex with men (MSM) with HIV / AIDS. This form is characterized by pain, the lesions can last weeks to months, and tends to be a persistent chronic ulcer.19,20 The risk of asymptomatic HSV
sheding was 4 times higher in HIV patients than without HIV. There is an inverse correlation between CD4 count and HSV-2 shedding and a direct correlation between plasma HIV ribonucleic acid (RNA) and shedding. In men, the lesion is on the glans penis or shaft of the penis, while in women it is on the vulva, perineum, buttocks, vagina, or cervix. Complaints are accompanied by pain, itching, dysuria, vaginal or urethral discharge, and pain in inguinal lymphadenopathy. Prodromal symptoms such as fever, headache, malaise and myalgia are common.

Figure 2. Vegetative ulcers of genital herpes in HIV patients.

Figure 3. Large and chronic ulcers in genital herpes patients with HIV.
**Diagnosis and work-up**

Although the classic clinical manifestations of HSV can be diagnosed with accuracy, they should still be confirmed by laboratory examination or biopsy, especially in HIV patients. The laboratory tests used were direct HSV detection from the lesion and indirect serologies (Tables 1-3). For acute lesions, take a specimen from vesicle fluid. For longer lesions, the diagnostic yield is very low. In this case, the patient is advised to return if new vesicles develop. For tissue specimen collection, a biopsy is performed on the edge of the ulcer.

**Laboratory examination**

1. **Direct diagnosis of HSV from clinical specimens**

1.1. **Cytologic examination**

This examination uses a Tzanck, Papanicolaou, or Romanovsky smear. The Tzanck smear is an easy, practical, and fast diagnostic test to detect HSV, but it is nonspecific because it cannot distinguish HSV-1, HSV-2, and varicella. This examination should be performed if the lesion forms vesicles. The swab is carried out from the base of the vesicle. A positive result shows typical multinuclear giant cells.

1.2. **Virus antigen detection**

When mucocutaneous lesions develop, the viral antigen of the lesion can be detected by direct immunofluorescence (IF), immunoperoxidase (IP) staining, or enzyme-linked immunosorbent assay (ELISA). Direct immunofluorescence (IF) is a rapid diagnostic test and can differentiate between types of HSV. HSV-1 and HSV-2 antigens can be detected by fluorescein-labeled type-specific monoclonal antibodies. The disadvantages of this examination are that the reagent is quite expensive, requires tools (fluorescent microscope), and is less sensitive than molecular examinations, with a sensitivity of 70-90% in symptomatic patients and decreasing in asymptomatic patients. Herpes protein can also be detected by ELISA examination using HSV-specific monoclonal or polyclonal antibodies. Compared to viral culture, ELISA sensitivity was ≥ 95% with specificity ranging from 62-100% in symptomatic patients.

1.3. **Virus isolation and typing on cell culture**

The most widely used cells for HSV isolation are primary human diploid fibroblasts and cell lines, such as MRC-5 cells (human fibroblasts), Vero cells (monkey kidney), Hep-2 cells (laryngeal squamous cell carcinoma), hamster kidneys, and rabbit kidney cells. The culture tube should be examined daily using a stereoscopic microscope to check for the characteristics of the cytopathic effect of HSV, which generally occurs 24-72 hours after inoculation. Characteristics of the cytopathic effect of HSV are elongated and scattered cell changes to become large, round, refractile, ballooning, numerous, and granular. There may also be focal cell necrosis, syncytia and multinucleated giant cells. This examination has a low sensitivity for recurrent lesions (25-50%) and dry ulcer or crusted lesions, whereas in primary and vesicle-shaped lesions, the sensitivity can up to 80-90%

| Collection site | Tools for sample collection | Collection method |
|----------------|-----------------------------|-------------------|
| Male skin or mucosal lesions (including the perianal area) | o Sterile needles | o Unroof the vesicles with a sterile needle |
| | o Sterile cotton-tipped, Dacron, or nylon-flocked swab | o Collect the content of the vesicles with a sterile swab and: |
| | o Microscope slides | |
Apply to a microscope slide (for immunofluorescence) or - Place on transport media for viral culture or NAAT

Male urethra
- Sterile cotton-wool, Dacron, or nylon-flocked swab
- Clean the external urethral ostium (OUE) with a swab moistened in saline
- Pull the prepuce backwards to avoid contaminating the specimen
- Put a sterile swab into the OUE (to a depth of 0.5-2 cm) and collect urethral exudates

Female skin or mucosal lesions (including the perianal area)
- Cotton swab and gauze
- Microscope slides
- Similarly as for male skin or mucosal lesions

Female urethra
- Sterile gauze swab (to remove excess discharge)
- Sterile cotton-wool, Dacron, or nylon-flocked swab
- Clean the vaginal introitus using sterile gauze swab
- Insert a sterile swab into the urethra (to a depth of 0.5 cm) to collect exudates

Cervix
- Vaginal speculum
- Sterile gauze swab
- Sterile cotton-wool, Dacron, or nylon-flocked swab
- Insert a vaginal speculum moistened with warm saline solution, and clean the cervical canal opening with a sterile gauze swab
- Insert a sterile cotton-wool swab or Dacron swab into the cervical canal (to a depth of 2 cm deep) and collect the material from lesions

2. Virus detection and quantification using molecular techniques

Nucleic Acid Amplification Test (NAAT) / Polymerase Chain Reaction (PCR) is the most sensitive test for detecting HSV, 11-71% superior to viral culture. The Nucleic Acid Amplification Test can also detect asymptomatic HSV shedding. This method of examination is often used and has replaced viral culture as the gold standard, because the procedure and transport are easy and readily available, more sensitive, and faster. However, the price of this inspection is still expensive.

Table 2. Direct laboratory methods for HSV diagnosis.

| Method                | Principle                                      | Specimens                                      | Sensitivity | Specificity | Advantage      | Loss                                      |
|-----------------------|------------------------------------------------|------------------------------------------------|-------------|-------------|----------------|-------------------------------------------|
| Cytological examination | Tzanck smear, Papanicolaou (Pap), or Romanovsky stains | - Skin or mucosal lesions                      | Low         | Low         | Inexpensive    | o Fresh lesions                           |
|                       |                                                | - Biopsy                                      |             |             |                | o Suboptimal sensitivity and specificity |
|                       |                                                | - Conjunctival or corneal smears               |             |             |                |                                           |
| Virus antigen detection | Detection of infected cells by direct immunofluorescence | - Smears tissue section                       | Moderate (genital ulcers: 70-90%; asymptomatic: <40-50%) | High (>95%) | Inexpensive    | o Fresh vesicles                          |
|                       |                                                | - Smear from base of vesicle                  |             |             |                | o Suboptimal sensitivity                   |
|                       |                                                |                                                |             |             |                | o Time-consuming                           |
|                       |                                                |                                                |             |             |                | o Labour intensive                        |

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| Test Type               | Specimens                                             | Sensitivity          | Cost and Time                                      | Additional Notes                                    |
|------------------------|-------------------------------------------------------|---------------------|---------------------------------------------------|------------------------------------------------------|
| Immunoperoxidase staining | - Swab                                                 | Moderate (80%)      | Reagent cost                                      | Fresh vesicles                                      |
|                        | - Smears from lesions                                 |                     | Rapid (<4 hours)                                  | Suboptimal sensitivity                              |
|                        | - Smear or vesicular fluid of exudate from base of vesicle | High (90%)         | Does not require specimen integrity               |                                                      |
|                        |                                                       |                     | Typing possible                                   |                                                      |
| ELISA                  | - Swab                                                 | High (genital ulcers:> 95%) | Fresh vesicles                                    | No viral typing                                      |
|                        | - Vesicular fluid or exudate from base of vesicle     | High (62-100%)      |                                                   |                                                      |
| Rapid test device      | - Swab                                                 | Unknown             | Unknown                                           | Point-of-care testing                                |
|                        | - Vesicular fluid or exudate from base of vesicle     |                     |                                                   | Not yet evaluated                                    |
| Viral culture          | - Swab                                                 | Low to high depending on clinical manifestations | Simplicity of sampling                             | Less sensitive than PCR                              |
|                        | - Skin lesions                                        | Vesicle fluid:> 90% | Classically, “gold standard” method               | Sample storage and transport conditions influence sensitivity |
|                        | - Vesicular fluid or exudate from base of vesicle     | Swab: 70-80%        | Currently, “preferred” test                       | Labour intensive                                     |
|                        | - Biopsy                                               | Mucosa: 30%         | Virus typing                                      | Expensive                                            |
|                        | - Mucosa without lesions                               | Ulcers: 95%         | Resistance phenotype testing                      | Specialized laboratories                             |
|                        | - Conjunctival / corneal smears                        |                     |                                                   | Results in 2-7 days                                  |
|                        | - Neonates                                             |                     |                                                   |                                                      |
| HSV cell isolation     | - Swab                                                 | High (~ 100%)       |                                                   |                                                      |
|                        | - Skin lesions                                        |                     |                                                   |                                                      |
|                        | - Vesicular fluid or exudate from base of vesicle     |                     |                                                   |                                                      |
|                        | - Biopsy                                               |                     |                                                   |                                                      |
|                        | - Mucosa without lesions                               |                     |                                                   |                                                      |
|                        | - Conjunctival / corneal smears                        |                     |                                                   |                                                      |
|                        | - Neonates                                             |                     |                                                   |                                                      |
### Molecular biology
Detection of HSV DNA and / or quantity by NAAT, such as PCR
- Swab
- Skin lesions
- Vesicular fluid or exudate from base of vesicle
- Mucosa without lesions
- Vitreous fluid
- Corticospinal fluids
- Blood

Highest (98%)  High (~100%)  High sensitivity
- Currently, “preferred” test
- Allows virus detection and typing in the same test
- Rapid
- Results in 24-48 hours, can be <3 hours
- Resistance genotyping
- Method of choice for CSF
- Specialized laboratories
- Not standardized
- Expensive

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#### Table 3. Virological and serologic approaches for the diagnosis of HSV-2 with or without lesions.22

| Initial assessment of genital lesions | Direct HSV-2 detection | HSV-1 specific IgG | HSV-2 specific IgG | Interpretation |
|-------------------------------------|------------------------|-------------------|-------------------|----------------|
| Positive                            | Positive or negative   | Negative          | o Acute HSV-2 infection  |
|                                     | Positive               | Positive          | o HSV-2 specific serologic reset in 15-30 days |
| Positive                            | Positive or negative   | Negative          | o Recurrent HSV-2 infection with HSV-2 infection |
|                                      | Negative               | Negative          | o Recurrent HSV-2 infection was acquired at least 6 weeks ago |
| No lesions                          | Cannot be applied      | Negative          | Negative          | o Patients are at risk for infection with HSV-1 and / or orolabial or genital HSV-2 infection |
|                                      | Positive               | Negative          | o Patients are at risk for infection with genital or orolabial HSV-2 |
|                                      | Positive               | Negative          | o Old HSV-1 and HSV-2 infections |

#### 3. Serologic examination is indicative of HSV diagnosis

This examination is recommended in patients with recurrent genital herpes, atypical features, resolved lesions, and negative HSV cultures. Serologic testing of HSV-2 in HIV patients is part of the initial HIV evaluation and helps identify asymptomatic HSV infection.15 HSV-2 infection can be diagnosed by
detecting a specific type of IgG against glycoprotein G HSV-2 with a sensitivity and specificity of more than 95% in HIV patients. IgG antibodies are generally negative in primary genital herpes because IgG can only be detected 2-12 weeks after symptom onset and persists. The HSV IgM test can detect the initial infection of a patient whose IgG level is not detected. IgM is positive during disease reactivation, but it is not specific for virus type. Due to these limitations, this examination is not recommended as a routine examination.

**Biopsy and histopathologic**

Initial changes appear to be swollen epidermal nuclei and appear slate-gray with peripheral chromatin clumping, homogeneous ground glass image accompanied by nucleus ballooning and cytoplasmic vacuolization (Figure 4 and 5). As the cells and plasma membrane are not intact, the infected keratinocytes coalesce and form multinucleated giant cells. These changes initially appear in the basal layer, then involve the entire epidermis layer. There are 2 degenerative changes to form intraepidermal vesicles, namely ballooning degeneration and reticular degeneration. In ballooning degeneration, cells become swollen and loss of attachment to surrounding cells forms acantholysis. This is characteristic of viral infection. Tzanck cells appear homogeneous with eosinophilic cytoplasm. Occurs mainly at the base of the vesicle and vesicles are formed intraepidermally. In reticular degeneration, epidermal cells become progressively swollen so that the cells become large and clear, then rupture and form vesicles. Reticular degeneration is not characteristic of viral vesicles or bullae and can be seen in other diseases such as allergic contact dermatitis. Eosinophilic intranuclear inclusion bodies appear in swollen cells. There is a large neutrophil and lymphocyte infiltrate.

Old lesions show lichenoid infiltrates or histiocytes with granulomatous inflammation. Verucous HSV infection is characterized by widespread viral infection of the epithelium involving the adnexes, including necrosis of the sebaceous glands, hair follicles, and sweat glands. Generally, verucous HSV infection is found in patients with CD4 counts <200 cells / mm3.

**Figure 4.** The histology of genital herpes shows ballooning degeneration, spongiosis and acanthosis.
Figure 5. (a) HSV infection shows intraepidermal bullae (b) Appears of multinucleated giant cells with nuclear molding and thickened chromatin margins.

Management

There is no drug that can eliminate HSV from the body. The goals of the management of HSV-2 infection are to relieve symptoms, stimulate reepithelialization, reduce HSV-2 transmission, prevent lesions and recurrence.\(^9,15\)

Non-pharmacology

Education

Counseling patients and sexual partners is an important treatment. The goal of counseling is to assist patients in treatment and prevent sexual and perinatal transmission. Some topics that can be discussed when counseling patients with HSV infection are:\(^18\)

- Course of disease with possible recurrent episodes, asymptomatic viral shedding, and risk of sexual transmission.
- Effectiveness of suppressive therapy in first-episode genital herpes patients to prevent recurrent symptomatic episodes.
- Episodic therapy to reduce the duration of recurrent episodes.
- Provide information to sexual partners about genital herpes and potential partners before having the first sexual intercourse.
- Potential sexual transmission of HSV that can occur during the asymptomatic period (asymptomatic viral shedding is more common with HSV-2 infection than HSV-1 and generally occurs within the first 12 months after infection with HSV-2).
- Abstinence of sexual activity when prodromal lesions or symptoms develop.
- The effectiveness of using latex condoms on men consistently and appropriately can reduce (not eliminate) the risk of transmission of genital herpes.
- Asymptomatic HSV infection.
- Risk of neonatal HSV infection.
- Increased risk of HIV acquisition in HSV-2 seropositive patients who are exposed to HIV (suppressive antiviral therapy does not reduce the risk of HIV transmission)

Pharmacology

There is no therapy that can eliminate the virus from the body. The 2017 European guidelines developed an algorithm for the management of herpes in immunocompromised patients (Figure 6). Episodic or suppressive systemic antiviral therapy is effective in reducing the clinical manifestations of HSV in HIV patients. In patients with advanced HIV, it is necessary to consider giving an antiviral dose 2 times the standard dose and if lesions persist on days 3-5, the dose may be increased. Based on the Centers for Disease Control and Prevention (CDC) 2015 (Table 4), the antiviral doses given to HIV patients with episodic genital herpes infection, namely: acyclovir 400 mg, orally, given three times per day for 5-10 days; or valaciclovir 1000 mg, orally, twice per day for 5-10 days; or famciclovir 500 mg, orally, twice per day for 5-
10 days. Treatment should be given for a minimum of 10 days or until the lesion is re-epithelialized. In severe and complicated cases, intravenous acyclovir is the mainstay of therapy with a dose of 5-10 mg / kg body weight every 8 hours for 2-7 days or until the lesions heal, followed by oral antiviral therapy for a minimum total of 10 days of total therapy.

In HIV patients, anti-HSV-2 suppressive therapy can be considered. Several studies have shown that acyclovir, valacyclovir, and famciclovir can lower plasma and genital HIV RNA levels, but the mechanism for this is unknown. The standard suppressive dose of acyclovir is quite effective. The suppressive therapy recommended by the CDC 2015 (Table 5) is acyclovir 400-800 mg, orally, two to three times per day; or valaciclovir 500 mg, orally, twice per day; or famciclovir 500 mg, orally, twice per day for at least 6-12 months. The risk of resistance increases with severity of immunodeficiency. If the genital herpes lesions are persistent or recurrent in the patient on adequate antiviral therapy, HSV resistance can be considered and virus isolation is required for sensitivity testing and a biopsy can be performed. In HIV patients who are resistant to acyclovir or its derivatives can be given intravenous foscarnet (vidarabine) 40-80 mg / kg body weight every 8 hours until reaching clinical resolution or intravenous cidofovir 5 mg / kg body weight once every week for 2 weeks.

Topical can be given imiquimod or cidofovir 1% applied once a day for 5 days. Topical antiviral therapy in genital herpes is not recommended because it is less effective than systemic therapy. Potassium permanganate compresses can be applied to ulcer lesions to prevent secondary infection.

Table 4. Episodic genital herpes therapy in HIV according to the CDC 2015.

| Drugs    | Dosage and method of administration | Duration                      |
|----------|------------------------------------|-------------------------------|
| Acyclovir| 3 x 400 mg orally                  | 5-10 days or until the lesions heal |
| Valacyclovir| 2 x 1000 mg orally              | 5-10 days or until the lesions heal |
| Famciclovir| 2 x 500 mg orally                 | 10 days or until the lesions heal |

Table 5. Suppressive therapy for genital herpes in HIV according to the CDC 2015.

| Drugs     | Dosage and method of administration | Duration             |
|-----------|------------------------------------|----------------------|
| Acyclovir | 2-3 x 400-800 mg orally            | Minimum 6-12 months  |
| Valacyclovir| 2 x 500 mg orally                | Minimum 6-12 months  |
| Famciclovir| 2 x 500 mg orally                 | Minimum 6-12 months  |
Prevention

Several efforts can be made to prevent HSV-2 transmission, including:\(^9\)

- Abstinence. All patients should be advised to avoid sexual contact at the time of prodrome, lesions, and for several days after recurrence.
- Limit the number of sexual partners.
- Avoid partners with a history of genital herpes.
- Appropriate and consistent use of condoms is a practical approach that is good enough to minimize the risk of acquiring genital herpes. However, this does not completely prevent the transmission of genital herpes.
- Vaginal and rectal microbicides can inactivate the virus at the port de entry, but this is still in the research stage.
- Antiviral therapy.
- Vaccine.

Vaccines against HSV have been widely developed, but until now there is no vaccine, either prophylactic or therapeutic, that has been approved. In experimental animals, vaccine-induced immunity fails to prevent viral replication in the genital tract and the presence of latent infection in the sensory ganglion remains a challenge.\(^9\)

Summary

Genital herpes is a sexually transmitted infection caused by HSV, especially type-2, is recurrent and lifelong. HSV-2 infection is the most common infection in HIV patients and can increase the risk of HIV acquisition 2 to 3 times. The main mechanism that occurs is the presence of CD4 cell recruitment and increased expression of important HIV receptors at the port de entry. Genital herpes patients with HIV have a high risk of developing chronic and severe genital ulcers with atypical features, prolonged healing, and
are easily resistant to treatment. The diagnosis can be made based on history, clinical manifestations, laboratory examination, and histopathologic biopsy.

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