

The Herpes Testing Toolkit

A Resource for Healthcare Providers

Genital herpes is a common viral infection, but it can be easily misdiagnosed and is often underdiagnosed. Clinicians can best serve their patients by using the correct laboratory test to provide a clear diagnosis along with providing education, reassurance, appropriate antiviral therapy, and resources for additional information and emotional support as needed.

The Herpes Testing Toolkit offers providers a summary of evidence-based information and expert opinion about testing and diagnosing genital herpes. This complex and dynamic topic is organized to simplify decision-making, assist with test interpretation and education and counseling. The toolkit also offers information and counseling messages for patients, both before testing and after diagnosis.

Additional information for providers and patients can be found at the website of the American Sexual Health Association at www.ashasexualhealth.org

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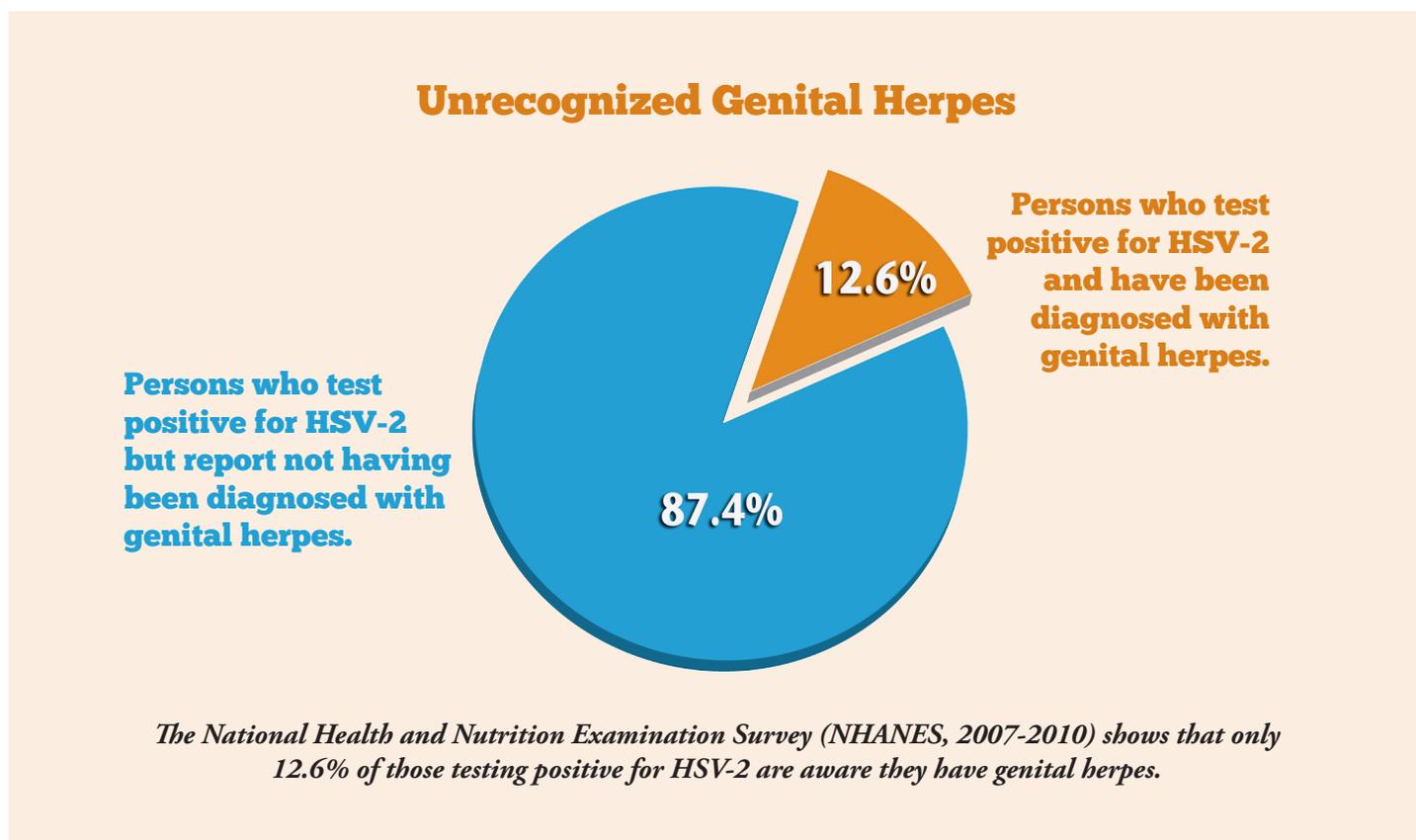


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Why is genital herpes testing so important?

Genital herpes is a common viral infection, caused by either **herpes simplex virus type 1 (HSV-1)** or **herpes simplex virus type 2 (HSV-2)**. It can be easily misdiagnosed and is often underdiagnosed. Clinicians can best serve their patients by using the correct laboratory test to provide a clear diagnosis along with providing education, reassurance, appropriate antiviral therapy, and resources for additional information and emotional support as needed.

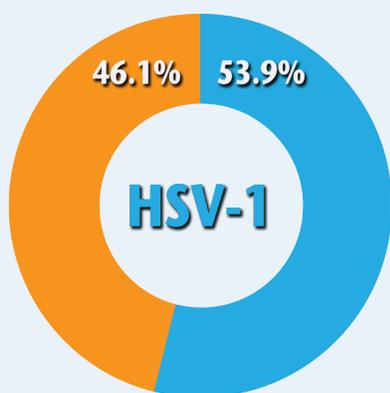
Diagnosing genital herpes by history and clinical examination, without laboratory confirmation, has several serious limitations: 1) 80-90% of people who have genital herpes report no history of signs/symptoms consistent with genital herpes; 2) 20% of people diagnosed by clinical visual exam alone have been found in two studies to not have genital herpes; and, 3) clinical presentations can be subtle, often without genital vesicles and ulcers, leading to misdiagnosis.



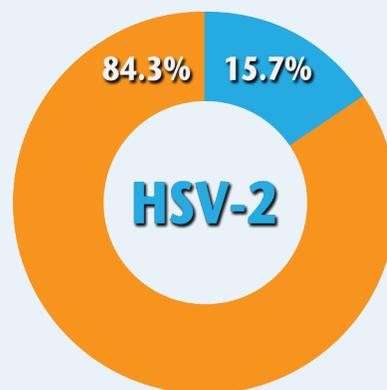
In the United States, more people have genital herpes than all other sexually transmitted infections combined—50 million people in total. Additionally, there are about one million new genital herpes infections each year due to HSV-2. Although the number of cases of genital herpes caused by HSV-1 is difficult to estimate, in some settings, up to half of first clinical outbreaks are due to HSV-1, usually through oral-to-genital transmission.

Both HSV-1 and HSV-2 cause lifelong infections; however, the natural history of genital infection is substantially different for the two types. Recurrences and asymptomatic viral shedding are much more common with HSV-2. Therefore, determining whether a patient has genital HSV-1 or genital HSV-2 infection is important as it can influence prognosis, treatment, and counseling messages. For example, the suppressive approach to treatment may be more appropriate for those with HSV-2 than for persons with HSV-1.

Seroprevalence of HSV-1 and HSV-2 in the U.S.



2010 HSV-1 seroprevalence: 53.9%



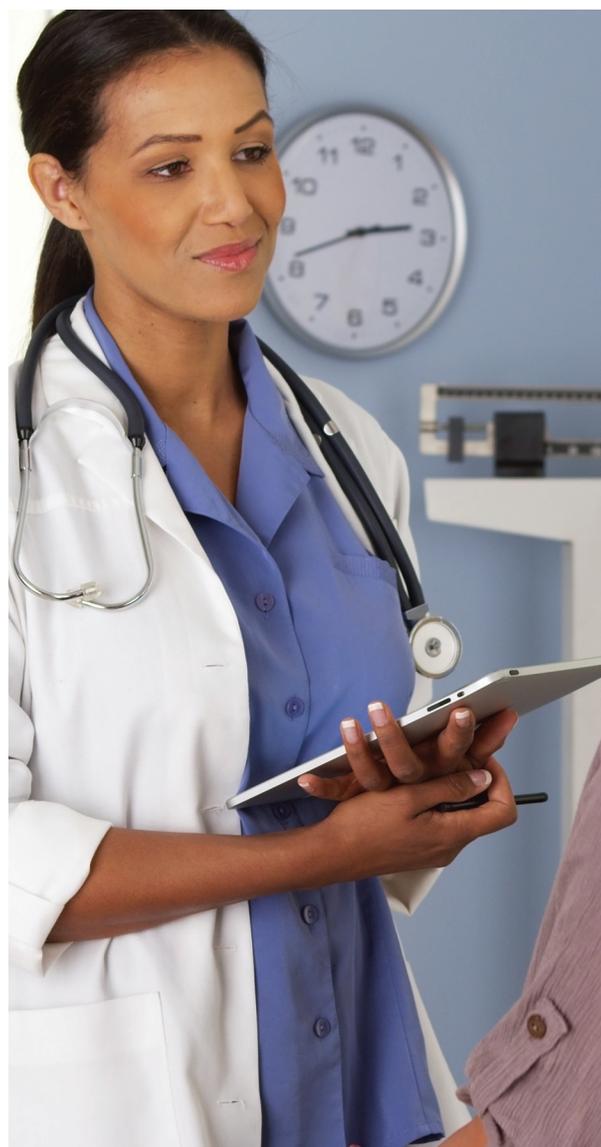
2010 HSV-2 seroprevalence: 15.7%

Who Should Be Tested?

Clinicians should make testing decisions based on individualized risk factors and patient preferences. Although there is some disagreement among experts as to which groups benefit most from serologic (blood) testing, there is general agreement that testing is significantly underutilized. As indicated by the clinical scenarios in the table on the following page, a wide range of patients are likely to benefit from the use of swab and/or type-specific serologic tests (Immunoglobulin G, or IgG, antibody tests).

Swab test options include **viral culture** and the more sensitive **polymerase chain reaction (PCR)**. These tests are most sensitive when obtained within 3–4 days of the start of an outbreak. Type-specific serologic tests detect the presence of antibodies to HSV, and can be performed in the presence or absence of lesions.

Serologic tests cannot determine the anatomic location of HSV disease (i.e., genital versus non-genital). However, there is general agreement that a positive HSV-2 serologic test indicates genital infection with a high degree of certainty. HSV-1 serologic tests are less helpful in determining the site of infection. More than half of the U.S. population has HSV-1 antibodies by late adolescence, primarily due to non-genital infection, thus HSV-1 testing may be less useful than HSV-2 testing. In general, patients with low or no likelihood of infection should not be tested. This includes children and those who have not had genital-to-genital or oral-to-genital sexual contact.



Candidate Patients for Type-specific Genital Herpes Tests

Testing Recommended	Swab Test (Viral culture or PCR)	Serologic Test (Type-specific antibodies)
Typical genital lesion	x	x
Clinical diagnosis with negative or no swab test		x
Atypical lesion (e.g. fissure, erythema)	x	x
Recurrent lower genital tract inflammation with no lesion (e.g. dysuria, burning, itching)		x
STI evaluation, no lesion		x
Sexually active patient requests test, no lesion		x
Sex partner of patient with genital herpes		x
Experts disagree on whether or not these patients should be tested		
HIV, no lesion		x
Sexual assault, no lesion		x
Pregnancy, no lesion		x
High risk populations (e.g., men who have sex with men), no lesion		x

What Test Should Be Used?

Many challenges face clinicians regarding the use of genital herpes laboratory tests, especially in the area of serologic test selection and timing of use. The following are important points to consider when selecting a test:

- Viral detection methods are the best methods for diagnosing genital herpes when lesions are present. However, due to declining sensitivity of viral culture as lesions begin to heal (after 3-4 days), a negative culture result does not rule out genital herpes. While not 100% sensitive, PCR tests provide greater sensitivity for both lesion and skin testing; compared to viral culture, PCR is three-fold more likely to isolate HSV (which may be especially valuable when sampling lesions that are healing). Turn-around time for HSV PCR is also quicker, typically a few hours versus several days with viral culture. PCR may be more costly than viral culture and not readily available in all locations.
- With either viral culture or PCR, to accurately detect virus the skin must be swabbed vigorously to obtain infected cells and the sample must be placed in the proper collection vial and transported under appropriate conditions. If the swab test is negative or not performed, a serologic test may be the next step.
- The type-specific serologic tests, while generally accurate, can only detect HSV antibodies after a person's immune response has made detectable antibody. Some patients develop antibodies a few weeks after lesions appear. Others require six weeks, and nearly all will develop antibodies by 16 weeks. Older, serologic tests that are not type-specific are inaccurate and should never be ordered.

- Type-specific serologic tests detect IgG (Immunoglobulin G) antibodies. The current STD Treatment Guidelines from the Centers for Disease Control and Prevention (CDC) state that accurate, type-specific assays for HSV-1 and HSV-2 should be based on HSV type-specific glycoprotein G (gG). Currently available IgM serologic tests can be falsely positive and should not be used to diagnose genital herpes.
- Type-specific serologic tests provide qualitative results. Thus, the exact value does not relate to the severity, reactivity, or other clinical characteristics of the individual's infection.



Confirmatory and Repeat Testing for Equivocal, Low-value Positive, or Improbable Results

Confirmatory testing is usually not necessary for swab tests or most serologic tests. However, false positive serologic tests occasionally can occur, which can be especially problematic when patients with a low likelihood of HSV infection are tested. Confirmatory serologic tests are indicated in several situations. In early infection, for example, serologic tests may be equivocal or have a low positive value. If persons have an equivocal test because they have only recently acquired herpes and are early in the development of antibodies, the equivocal result may be resolved by repeat testing with a second specimen collected one month after the initial specimen. Alternatively, a second sample can be drawn and sent for a second test using an alternate assay such as the Western Blot. Available from the University of Washington, the Western Blot is useful in confirming HSV-1 and HSV-2 serologic results.

Interpreting Test Results

Swab Viral Tests (Viral Culture and PCR)

Positive: Swab tests have the advantage of identifying both anatomic location of the infection and viral type (though typing often needs to be specifically requested). A genital culture positive for HSV-1, for example, provides definitive diagnosis of genital herpes due to HSV-1. HSV-1 has been increasing as a cause of first episodes of genital herpes. Serologic testing is not necessary in a patient with a recurrent genital lesion who has a prior positive HSV culture that has been typed.

Negative: Swab test results may be negative for many reasons. A negative swab test does not rule out genital herpes. Sensitive swab tests performed early in the next suspected outbreak or type-specific serologic testing may be useful 6-12 weeks after the most recent exposure.

Serologic Tests for HSV-2

HSV-2 Positive: A positive test for HSV-2 indicates genital infection, as orofacial infection alone is rarely due to HSV-2. Patients who are diagnosed by serologic testing but have no symptoms should be educated about mild, often unrecognized, symptomatic genital herpes disease, asymptomatic viral shedding, and risk of transmission to uninfected sex partners. Confirmatory or repeat testing is usually not necessary, unless, for example, the ELISA value is a low positive in the absence of symptoms. There are various definitions for what constitutes a low positive value, depending on the particular serologic test.

HSV-2 Equivocal: An equivocal result may be resolved by repeat testing with a second specimen collected one month after the initial specimen. If repeating the original serologic test does not resolve the equivocal result, then a confirmatory test should be considered. Rarely, seroconversion can take as long as 6 months after acquisition of infection.

HSV-2 Negative: A negative serologic test for HSV-2 usually means no HSV-2 infection, unless the infection was acquired recently. Because some people can take months to seroconvert, these results should be interpreted cautiously in someone with recent exposure, high-risk behavior, or a new lesion. A repeat test 3-4 months after the initial test may be helpful.

Serologic Tests for HSV-1

HSV-1 Positive: Slightly more than half of U.S. adults have antibody to HSV-1, so a positive test is not unusual nor does it imply genital herpes, since most people with HSV-1 antibodies have orofacial infection (cold sores or fever blisters). However, an increasing percentage of new genital herpes infections in young adults appear to be caused by HSV-1. A person with no history of cold sores who has a positive HSV-1 antibody test cannot know for certain where they are infected. These patients should be told that if they develop signs or symptoms in either the oral or genital area, they should come into the office for an evaluation to determine if these are herpetic.

HSV-1 Equivocal: An equivocal result may be resolved by repeat testing with a second specimen collected one month after the initial specimen. If repeating the original serologic test does not resolve the diagnosis, then a confirmatory test should be considered.

HSV-1 Negative: A negative serologic test for HSV-1 usually means no infection with HSV-1 unless it was acquired recently. Of note, the sensitivity of the Focus HSV-1 ELISA is slightly lower than that of the HSV-2 assay, so the ELISA test may miss almost 1 out of 10 people infected with HSV-1. New acquisition of genital HSV-1 infection is of particular concern for pregnant women without HSV-1 antibodies due to high risk of vertical transmission to the neonate.

Information for Patients—Before Test Results

Genital herpes is a common infection caused by one of two viruses: **herpes simplex virus type 1 (HSV-1)** or **herpes simplex virus type 2 (HSV-2)**.

Cold sores or fever blisters (oral herpes) are caused by HSV-1. Canker sores are *not* oral herpes. If you have oral herpes, you can transmit this infection to partner(s) by giving them oral sex.

Genital herpes is transmitted by **direct skin-to-skin contact** through sexual activities, such as penile-vaginal intercourse, oral-genital contact (oral sex), or penile-anal insertion (anal sex).

Almost 9 out of 10 people who have genital herpes do not know it, because signs and symptoms can be mild or confused with other conditions.

The **virus can be transmitted (spread) even when there are no signs and symptoms**. This occurs when virus is present on the skin without noticeable lesions. Although there are no signs or symptoms, it is potentially contagious.

Signs or symptoms may appear within a few weeks after first becoming infected. **Not everyone who becomes infected with herpes has symptoms**, and in some, symptoms can first appear anywhere from months to years after the initial infection.

Though they vary greatly from person to person, symptoms or signs of an outbreak can include: sores or blisters (lesions) along with fever and/or swollen glands. A first outbreak may take two or three weeks to heal, but later outbreaks heal more quickly, often in a matter of days.

There are **different types of tests to detect herpes infection**. Some tests (swab or DNA tests) require visible sores to look for the virus. Type-specific serologic tests (blood tests) can detect antibodies that build up in the blood in response to the virus and indicate infection.

Test results that differentiate between HSV-1 and HSV-2 are helpful in making a definitive diagnosis and deciding on a treatment strategy, if appropriate. An HSV-1 positive blood test does not tell whether one has oral herpes or genital herpes, only that one has HSV-1 infection.

In most cases, there is **no way to tell who gave you the infection** or how long the infection has been present.

For some people, a herpes diagnosis carries a significant emotional burden, usually short-lived. There are **resources for patients** who would like additional support, such as the American Sexual Health Association website at www.ashasexualhealth.org.

There are **several approaches to managing herpes**. Antiviral medications can reduce viral shedding, frequency of outbreaks, transmission to partners, and for pregnant women, to newborns. Correct and consistent use of condoms also reduces the chance of transmission.

Acquiring HSV for the first time late in pregnancy presents the most risk for the newborn. For this reason, a pregnant woman who does not have herpes and who has a partner with either oral or genital HSV is encouraged to avoid both intercourse and receiving oral sex during the third trimester.



Information for Patients—After Positive Test Results

HSV-1 is the most common type of herpes infection; over half of the U.S. population has this infection. HSV-2 is also very common; almost 1 in 6 people in the U.S. have HSV-2, but most do not know they have it.

HSV-1 can be found in the oral or genital area or both, and can be transmitted to others in their oral or genital areas. Genital HSV-1 usually results in fewer outbreaks than HSV-2. **HSV-2 is usually found in the genital area** and is usually transmitted to others in their genital area.

Genital HSV-1 can be acquired by receiving oral sex from someone who has oral HSV-1, or by having genital-to-genital or genital-to-anal skin contact with someone who has genital HSV-1. Genital HSV-2 is usually acquired by having genital-to-genital or genital-to-anal skin contact with someone who has HSV-2.

The herpes virus can live inside the body without symptoms or signs for many years. It is difficult to know how long you have had herpes or who gave it to you.

Even though there may be no noticeable signs or symptoms, people with genital HSV-1 or HSV-2 may shed virus from their skin (called asymptomatic viral shedding) and, as a result, **can be contagious at any time.** There is no easy way to know for sure when this is happening.

Symptoms of HSV-2 may include itching or tingling, flu-like symptoms (e.g. fever), and/or visible, sometimes painful bumps (lesions). **Not everyone who has HSV-2 infection has symptoms they recognize.**

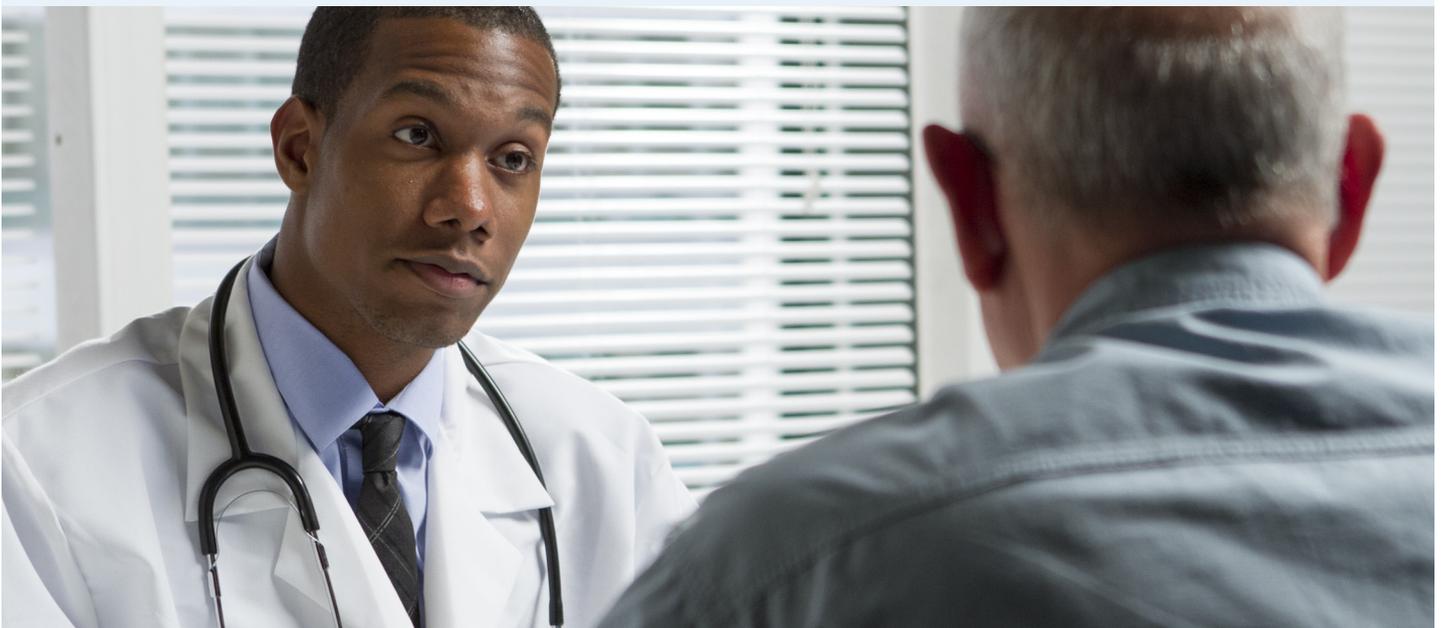
The **first outbreak often has the most severe symptoms** because the body's immune system has not developed a response to the virus. The first outbreak may occur months to years after the initial infection.

There are **treatment options available** to reduce frequency and duration of outbreaks, asymptomatic viral shedding, and transmission. Antiviral medications can be taken daily to decrease the number of outbreaks you get and to reduce the risk of transmitting to a partner. They can also be used when an outbreak occurs to decrease the length of the outbreak. Using condoms correctly and consistently has been found to reduce transmission.

Asking your current and future sexual partners to **get tested** can let you know whether they are at risk or whether they are already infected. If they have the same HSV type that you do, neither of you can be re-infected with the same type of virus and transmission between you is no longer a concern.

Discussing sexually transmitted infections with partners has also been associated with reduced transmission, perhaps because **couples can discuss safer sex practices** such as using condoms and avoiding direct sexual contact during outbreaks or if experiencing tingling sensations or other symptoms before an outbreak.

It is uncommon for herpes to cause problems with pregnancy. It is important, however, to talk to your healthcare provider about your herpes diagnosis or your sex partner's herpes diagnosis.



Expert Q&A

In this expert Q&A, **Leandro Mena, MD, MPH**, and **James B. Brock, MD**, of the University of Mississippi Medical Center explain the best uses of the different tests for herpes that are available to diagnose patients with and without symptoms.

Viral Culture

An HSV culture is often the test of choice for patients with symptoms, like lesions. While a culture for HSV is reliable if positive, can't there be issues with false negatives if lesions are healing?

Yes, culture has been the traditional method for diagnosis of herpes simplex infections. However, viral culture is typically only positive in early lesions, and they are not very useful once lesions begin to heal. If a culture is performed on a healing lesion and is negative, you may still have a herpes infection. Use of culture is very low if no active lesions are present. Herpes virus can be cultured from more than 90% of fluid-filled lesions, but ulcers can be cultured only 70% of the time, and only 27% can be cultured at the crusting stage.

How reliable is an HSV culture test during an initial outbreak versus a recurrent episode?

Viral culture is much more reliable during a first-time infection, rather than a recurrent infection because the amount of virus present is much higher. Even in an initial outbreak, though, a negative culture does not mean that you absolutely do not have a herpes infection.

Do labs automatically type an HSV culture for HSV-1 and HSV-2? Given that genital HSV-1 is increasingly common, is this a discussion patients need to have with their provider?

If herpes simplex virus is isolated in viral culture, it should be routinely typed. Patients have a right to their laboratory information, and HSV typing may be useful to know because HSV-2 is more likely to cause recurrent genital herpes.

DNA Tests

How do PCR tests for HSV stack up to culture tests?

PCR is 3-4 times more likely to isolate herpes simplex than viral culture. When sores are healing or absent, PCR may still be able to isolate virus when culture is not very useful. Also, viral culture requires proper handling of specimens by keeping them cold and processing them soon after sampling, which is not as much of an issue with PCR. PCR can also be run much more quickly (2 hours), whereas culture requires several days to grow.

Why aren't HSV PCR tests used more commonly?

Viral culture remains a recommended test-of-choice along with PCR. PCR is a newer test and may be more costly. Physicians may also be unaware that PCR for HSV is available and more likely to isolate the virus.

Blood Tests

Would you comment on the value of routine HSV testing with patients who have a history of symptoms but who have never been diagnosed?

In patients with no active lesions, PCR and culture are of limited value. Negative antibodies to HSV-1 and HSV-2 may be useful to argue against HSV infection as the cause of those symptoms. However, most individuals have HSV-1 antibodies and are difficult to interpret. A positive antibody test to HSV-2 would suggest genital herpes infection as the cause of the symptoms.

What about blood tests for someone with a current or recent partner who has HSV-2?

If your partner has HSV-2, serology may be useful to know whether or not you have been exposed in the past to HSV. A negative antibody test to HSV-2 would suggest that you are at risk for future infection with HSV-2 if you have an infected partner.

Should pregnant women be tested for HSV?

Transmission of herpes to newborns is highest in women with recent HSV infection. Therefore, pregnant women with negative serology would be considered at risk for HSV infection and should be counseled to abstain from sex in the third trimester with a partner known to have herpes. However, the same recommendation is applied to pregnant women not known to have clinical herpes without serologic testing.

What about routine HSV testing for those who are HIV-positive or in a relationship with someone who has HIV?

HSV infection in HIV-infected patients, especially those with weakened immune systems before start anti-retroviral therapy, tends to be more severe and more prolonged, and recurrent HSV infection is more common in HIV-infected patients. If an HIV-infected patient has positive serology for HSV-2, suppressive antiviral therapy may be

offered to prevent HSV recurrence. Also, patients with genital herpes are at increased risk for HIV infection, and the risk is still increased even with antiviral treatment for HSV. Treatment of the HIV-infected partner with HIV antiretrovirals, however, would be expected to decrease HIV transmission.

Are there others that might benefit from testing?

Screening by HSV serology for patients that are high risk for infection, including those with multiple sexual partners and men who have sex with men (MSM), can be considered. A negative HSV-2 serology would suggest future risk for infection with HSV-2. Also, patients with recurrent genital symptoms and a negative HSV culture or PCR may have serologic testing performed. Negative HSV-2 serology would make genital herpes less likely.

HSV blood tests are based on detecting antibodies, which take a weeks or even months to develop at detectable levels. How long should someone wait to be tested?

If a patient feels that they were recently exposed, acute (now) and convalescent (later) serology can be obtained. Negative results now and positive results in 4-6 weeks would suggest a recent infection with HSV.

When someone receives results from their HSV blood test they're given a number called an index value (measuring the antibody levels detected). This is a source of confusion for patients who have intermediate or "low positive" index values. What are the numerical cutoffs for when you feel confident that someone has a solid positive or negative test result?

An index value less than 1.1 should be considered negative, and above 3.5 should be considered positive.

So when somebody has a low positive, talk about confirmatory testing. How long should they wait and which test(s) should be used?

Index values in the middle range are difficult to interpret, as false positives and false negatives can occur in this range. If a "low positive" index value is encountered, testing can be repeated with another method, including the Western Blot, Biokit Rapid assay, and the Focus recombinant inhibition HSV-2 ELISA (from Quest). Also, those with recent infection may not have had time to develop antibodies. By 3 weeks, about half of infected individuals will have detectable antibodies, 70% by 6 weeks, and almost 100% by 6 months. Waiting 6 months should be sufficient time to allow for antibody production.

Explain the difference between HSV IgG tests and IgM tests. how does this figure into the idea of a type-specific HSV blood test?

IgM antibody is usually the first antibody that is produced by the body during an infection and tends to decrease over time. On the other hand, IgG levels increase weeks after an infection but may remain positive for years to life.

Should HSV IgM tests ever be used clinically?

IgM antibody does not distinguish HSV-1 from HSV-2 infection and is not very useful clinically.

Can an HSV blood test ever distinguish a recent from a longer-standing infection?

Positive antibody tests indicate exposure and may remain positive for life. If a patient has had a negative antibody test in the past and now has a positive antibody, then the exposure likely occurred between the time of those two tests. A negative antibody test now and a positive antibody test in the near future suggests a recent infection.

Many adults have HSV-1 in the way of oral herpes they may have experienced since childhood. An increasing number of genital herpes infections are due to HSV-1 though. When is there value to having an HSV-1 blood test?

It is true that most adults will have a positive HSV-1 antibody test. This does not help to distinguish prior exposure from current infection with HSV. A negative HSV-1 antibody test may or may not be reliable depending on the type of test that was done, particularly the HerpeSelect HSV-1 ELISA. However, a negative HSV-1 antibody by another assay may suggest risk for infection with HSV-1 in the future. HSV-1 isolated by culture or PCR in a genital site is strongly suggestive of HSV-1 genital herpes, on the other hand.

How often does HSV-1 and HSV-2 co-infection occur at the same site? Are there any implications here regarding testing?

It is unclear how often HSV-1 and HSV-2 infection occurs at the same site, but genital HSV-1 infection rates are increasing and may account for up to 50% of new genital herpes infections now. However, it is much less likely to cause recurrent genital herpes, and HSV-2 accounts for about 90% of recurrent genital herpes infections. If a patient has recurrent genital herpes and positive serology for HSV-1 and HSV-2, it is likely that HSV-2 is the culprit of the recurrent genital herpes.



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