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Serologic Screening for Genital Herpes Infection: An Evidence Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, (i.e., in the context of available resources and circumstances presented by individual patients).

The final report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Structured Abstract

Purpose: To assess the benefits and harms of serologic screening and preventive interventions for genital herpes simplex virus (HSV) infection in asymptomatic adults, adolescents, and pregnant women.

Data Sources: PubMed/MEDLINE, the Cochrane Library, EMBASE, and trial registries through March 31, 2016 and reference lists of retrieved articles.

Study Selection: Two investigators independently selected English-language studies using a priori criteria. Eligible studies included randomized controlled trials (RCTs) of screening or preventive interventions for genital HSV infection, RCTs assessing the benefits or harms of preventive interventions aimed at reducing transmission or future symptomatic episodes of genital herpes, studies evaluating accuracy of serologic screening tests for HSV-2, systematic reviews (and studies published after eligible systematic reviews) evaluating the accuracy of serologic tests or harms of screening, multi-institution antiviral medication pregnancy exposure registries, and trials or observational studies assessing the harms of serologic screening.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for all included studies using predefined criteria.

Data Synthesis: We included 18 studies. No RCTs compared screening with no screening. Eleven studies assessed the accuracy of one or more serologic tests for HSV-2; most of these 11 studies enrolled populations with a high prevalence of HSV-2 (>40%) and did not describe whether participants had current or past symptoms consistent with genital herpes. Ten studies assessing the accuracy of HerpeSelect® HSV-2 (n=6,537 participants) provided sufficient data to estimate sensitivity and specificity at the manufacturer's cutpoint (1.1); pooled estimates of sensitivity and specificity were 99 percent (95% CI, 97 to 100) and 83 percent (95% CI, 72 to 90), respectively. Seven studies (n=5,517 participants) also assessed the accuracy of HerpeSelect® at higher cutpoints (ranging from 2.2 to 3.5); pooled estimates of sensitivity and specificity were 96 percent (95% CI, 94 to 97) and 89 percent (95% CI 80 to 94), respectively. Four studies (n= 1,512 participants) evaluated the accuracy of BiokitHSV-2 Rapid Test; pooled estimates of sensitivity and specificity were 84 percent (95% CI, 73 to 91) and 95 percent (95% CI, 93 to 97), respectively. Use of HerpeSelect® at the manufacturer's cutpoint in a population of 100,000 with a prevalence of HSV-2 of 16 percent (the seroprevalence in the general U.S. adult population with unknown symptom status) would result in 15,840 true positive tests and 14,280 false positive tests (positive predictive value = 53%). Serologic screening for genital herpes is associated with psychosocial harms, including distress and anxiety related to positive test results. Two RCTs compared preventive antiviral medications with placebo in nonpregnant adults who were HSV-2 seropositive and reported on symptoms consistent with genital herpes over 6 to 8 weeks; these studies found inconsistent results. Two RCTs compared preventive antiviral medications with placebo among discordant couples to prevent HSV-2 transmission; these studies were heterogeneous and found inconsistent results.

Limitations: Most studies assessing the accuracy of serologic screening tests were conducted in African countries where the prevalence of HSV-2 is much higher than in the United States. The

true prevalence of asymptomatic HSV-2 infection in the United States is unknown. We identified no eligible studies that assessed behavioral counseling interventions in adults, adolescents, or pregnant women with asymptomatic or unrecognized genital herpes. Two RCTs assessing preventive antiviral medications in populations with asymptomatic HSV-2 were heterogeneous and followed participants over a short time (6 to 8 weeks). Two RCTs assessing preventive antiviral medications in discordant couples were heterogeneous; one enrolled generally healthy couples discordant for both HSV-2 and HIV from African countries.

Conclusions: Serologic screening tests are associated with a high rate of false-positive results in populations with a prevalence of HSV-2 similar to that in the U.S. adult population. Serologic screening for genital herpes is associated with potential psychosocial harms, including distress and anxiety. Current evidence from controlled trials does not establish whether or not preventive antiviral medication for asymptomatic HSV-2 infection has benefit.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to update its 2005 recommendation on serologic screening for genital herpes simplex virus (HSV) infection. In 2005, the USPSTF recommended against routine serological screening for HSV in asymptomatic adolescents and adults (Grade: D recommendation) and asymptomatic pregnant women at any time during pregnancy to prevent neonatal HSV infection (Grade: D recommendation).[1] The purpose of this report is to evaluate the evidence on benefits and harms of serologic screening for asymptomatic HSV infection, and to review the performance characteristics of HSV serologic tests.

Condition Definition

Genital herpes is a viral sexually transmitted infection caused by one of two HSV subtypes: HSV-1 or HSV-2. The term "genital herpes" is most often used to describe a range of signs and symptoms of HSV infection in the area innervated by the sacral nerve ganglion, typically genital or perianal lesions.[2,3] **Table 1** describes the categories of genital HSV infection and the common clinical manifestations for each category. We use the term "asymptomatic" to refer to populations in whom serum antibody is present, but there is no history of symptomatic occurrence.

Etiology and Natural History

Genital HSV acquisition occurs predominantly through sexual activity—genital-to-genital or orogenital contact—and viral latency is established in the sacral ganglia followed by viral reactivation and recurrent local disease.[3,4] HSV-2 accounts for the majority of prevalent cases of genital herpes and is more likely to cause frequent symptomatic recurrences and more severe symptoms than HSV-1 infection.[2,5,6] HSV-1 is most commonly associated with orofacial herpes symptoms (e.g., "cold sores") and usually acquired during childhood. The incubation period for genital HSV of either viral type ranges from 1 to 12 days, and is often followed by an occurrence of symptoms (primary infection).[2,3] Many persons will experience marked signs and symptoms during primary infection, including bilateral lesions along with regional lymphadenopathy, headache, fever, malaise, and other symptoms. Primary infection may also be mild or entirely asymptomatic.[7]

Recurrences may be symptomatic or asymptomatic (i.e., subclinical viral shedding only), and are common following symptomatic primary infection. An estimated 70 percent to 90 percent of patients with clinical first episodes of genital HSV-2 will experience recurrences in the first year and many will have multiple symptomatic episodes per year (the average number is 4, but some patients may have 10 or more).[3,8] Recurrences are more common with HSV-2 than HSV-1.[7,9] Over time, the average number of symptomatic recurrences per year declines.[7,8] Recurrences (as

well as primary infection) can be associated with "nonclassical" signs and symptoms that may be misdiagnosed or confused with other conditions (e.g., yeast infections, fissures, urinary tract infections, irritation related to sexual intercourse).[7,10-12] In addition, episodic subclinical viral shedding (i.e., viral shedding in the absence of genital lesions) at skin and mucosal sites occurs in both men and women, leading to the potential for transmission in the absence of symptoms.[11,13]

In women who have a prior history of symptomatic genital herpes, nearly 75 percent will have at least one recurrence during pregnancy, and about 14 percent will have prodromal symptoms or clinical recurrence at delivery.[14,15] Most cases of neonatal HSV are transmitted from mother to fetus by direct contact with virus in the genital tract during birth.[16]

Risk Factors

Risk factors for genital HSV infection have primarily been described using studies of seroprevalence (e.g., NHANES); the independence of factors such as age, sex, and number of sexual partners is unclear. Risk factors for genital herpes are discussed in more detail in **Appendix A**.

Among pregnant women, factors associated with seroconversion (i.e., incident HSV-2 infection) include younger age, being unmarried, and the occurrence of other sexually transmitted diseases.[17] Perinatal transmission requires that the HSV virus be present in the genital tract of the mother at the time of delivery, either symptomatically or asymptomatically. The risk of vertical transmission is related to the presence of maternal antibodies to HSV and the route of delivery (higher with vaginal delivery versus Cesarean section).[16,18] Women who acquire HSV near the time of delivery are at higher risk for vertical transmission compared with women who have antibodies to HSV-1, HSV-2 (or both).[7,16] Additional risk factors for development of neonatal HSV among infants born to women with positive HSV cultures obtained at delivery include the use of fetal scalp electrodes, HSV isolated from the cervix (versus vulva only), and premature delivery (< 38 weeks).[16]

Prevalence and Burden

Genital herpes is one of the most prevalent sexually transmitted infections in the United States. Data from the 2005-2010 National Health and Nutrition Examination Survey (NHANES) estimated the seroprevalence of HSV-2 among people 14 to 49 years of age at 15.5 percent.[19] Estimated seroprevalence rates vary by age, sex, race and ethnicity, and geographic region. Among those 14 to 19 years of age, HSV-2 seroprevalence is estimated to be 1.4 percent compared with 26.1 percent in people 40 to 49 years of age.[19] Women have a higher estimated seroprevalence than men (20.9% vs. 11.5%), which is attributed to anatomic factors predisposing women to be more susceptible to HSV-2 infection than men. Men who have sex with men have a HSV-2 seroprevalence similar to that of women (20.7% among men who have ever reported sex with another man, and 23.2% for those who reported it in the last 12 months).[20] Non-Hispanic blacks have the highest estimated seroprevalence of HSV-2 infection at 39.2 percent, which is three times that of non-Hispanic whites (12.3%).[19] NHANES data from 1988 to 2004 estimated

that 35 percent of pregnant women were seropositive for HSV-2.[21,22]

HSV-1 infection is common. The seroprevalence of genital herpes due to HSV-1 alone is uncertain because a positive serologic test for HSV-1 can signify oral infection only, genital infection only, or both. NHANES data from 2005-2010 NHANES estimates the HSV-1 seroprevalence at 53.9 percent.[6] Historically, HSV-1 is transmitted in childhood via oral secretions. However, studies in the United States and Europe have documented declining rates of HSV-1 acquisition during childhood. In the United States (based on NHANES data), the seroprevalence of HSV-1 among younger cohorts (people 14 to 19 years of age) has greatly declined over the past few decades.[6] Among subgroups of NHANES participants, a higher proportion of persons infected with HSV-1 (but not with HSV-2) reported having been diagnosed with genital herpes in 1999–2004 compared with 1988–1994 (1.8% versus 0.4%, respectively; $p<.001$).[23]

In addition, some data suggest that HSV-1 is a more common cause of incident genital herpes than HSV-2.[24-29] For example, in the control arm of a herpes vaccine trial (N=3,438), women who were seronegative for HSV-1 and HSV-2 had a higher incidence of HSV-1 (2.5 per 100 person-years) compared with HSV-2 (1.1 per 100 person-years) infection over a 20-month period.[24] Most infections (74% of HSV-1 and 63% of HSV-2) occurred without recognized signs or symptoms of herpes disease. Of the 54 participants presenting with symptomatic HSV, 33 had HSV-1 disease (5 oral, 24 genital, 4 both genital and oral) and 21 had HSV-2 disease (all genital).[12,24,30]

Genital HSV infection can lead to both acute and chronic morbidity. **Table 1** outlines the clinical features of primary, nonprimary, and recurrent infection. Nonprimary first episode infection is associated with fewer lesions and less systemic symptoms than primary infection, presumably because the presence of antibodies against one HSV type offer some protection against the other.[31,32]Acute primary (or nonprimary) infection can be severe and associated with multiple, bilateral, ulcerating, pustular lesions that resolve after a mean of 19 days.[31] Extragenital complications can also occur; in a study of 268 adults with primary first-episode genital herpes, extragenital complications included aseptic meningitis (8%), urinary bladder retention due to sacral autonomic nervous system dysfunction (2%), secondary yeast infections (11%), and distant skin lesions (20%).[31]

Genital HSV-2 infection is highly prevalent among HIV-infected patients. Epidemiologic studies suggest that incident and prevalent genital HSV-2 increases the risk of HIV acquisition;[33-36] potentially due to disruption of the genital mucosal barrier or alteration of immunologic factors (or both). In addition, genital HSV-2 infection may contribute to the risk of HIV transmission by increasing HIV genital shedding (particularly at sites of genital ulcerations).[37] Whether this association results from similar modes of acquisition or to biologic interactions between the two viruses has been a topic of debate. So far, clinical trials have not supported a role for HSV-2 suppressive therapy in preventing HIV acquisition among HSV-2 seropositive HIV uninfected persons.[38,39]

Approximately half of people with symptomatic recurrences have prodromal symptoms before eruption of genital lesions (e.g., local mild tingling, shooting pains in the buttocks, legs and

hips).[32,40] Because of the chronic nature of genital HSV, those with symptomatic infections often experience psychological distress following diagnosis. Common worries for patients include the potential for ongoing symptomatic episodes, the impact of herpes on sexual relationships, questions about transmission to sexual partners, and management of herpes in pregnancy.[41]

Genital HSV infection during pregnancy is of particular concern because of the risk of transmission to the infant during delivery. Vertical transmission typically occurs by direct contact with the virus in the genital tract during delivery. Estimated rates of neonatal infection with HSV range from 1 out of every 3,200 to 10,000 live births in the United States.[16,42-44] One large multistate U.S. study found an overall incidence of 9.6 cases per 100,000 births in 2006;[42] rates varied significantly by geographic region, race, and insurance status. Mothers with Medicaid had higher rates of neonatal infection during delivery than mothers with private insurance or managed health care (15.1 cases vs. 5.4 cases per 100,000 births).[42] The most recent estimate is based on a clinical laboratory reporting system initiated in New York City in 2006.[45] Between April 2006 and September 2010, 76 cases were detected and the average incidence was estimated at 13.3 per 100,000 live births (or 1 per 7519 live births).[45] Most reported cases were laboratory confirmed (91%); 41 percent (28 cases) were HSV-1 and 39 percent (27 cases) were HSV-2 (20% of cases were not typed).[45]

Vertical transmission of HSV can lead to significant fetal morbidity and mortality. Of newborns diagnosed with neonatal herpes, approximately 45 percent of cases involve infection of the skin, eye, and mucous membranes; 30 percent develop the encephalitic form of neonatal herpes (which presents with nonspecific signs and symptoms such as fever, lethargy and irritability, or poor feeding); and 25 percent develop disseminated disease.[46] Many survivors of CNS neonatal herpes infection are left with long-term neurodevelopmental impairment.[47] Approximately 30 percent of infants with disseminated disease and 4 percent with central nervous system disease will die from HSV infection.[32]

Rationale for Screening

In theory, serologic screening to identify unrecognized HSV-2 infection followed by appropriate counseling or treatment could prevent transmission (to partners and neonates) and reduce future morbidity from symptomatic recurrences. Episodic or suppressive antiviral treatment for HSV-2 infection may be prescribed for HSV-2 to reduce symptomatic episodes and shedding. In pregnant women, serologic screening to identify seronegative women followed by appropriate counseling could reduce neonatal HSV infection given that women who acquire HSV late in pregnancy (and who are seronegative at delivery) are at highest risk for vertical transmission.

Several U.S. Food and Drug Administration (FDA)-approved type-specific HSV serologic tests rely on glycoprotein-G to distinguish between HSV-1 and HSV-2 antibodies; however, after exposure, it may take 6 weeks for antibody response to occur.[48] Since HSV-2 rarely causes infection outside the anogenital region, the presence of HSV-2 antibodies in serum can be interpreted as an indicator of genital herpes infection.[49] For people without symptoms (e.g., no genital lesions), the HSV Western blot is considered the gold standard for the diagnosis of herpes via serology. Although the Western blot can be obtained by sending samples to the University of

Washington Virology lab, this test is not commercially available as a confirmatory test for persons who screen positive for HSV-2 on an FDA approved commercially available serologic test. Genital HSV-1 infection cannot be diagnosed using serologic tests; HSV-1 is highly prevalent and these tests cannot determine the site of infection. For people with genital lesions, viral culture and polymerase chain reaction (PCR)-based testing are the preferred tests to confirm a diagnosis of genital herpes.[50] These tests are not recommended in people without genital lesions given that subclinical viral shedding is intermittent.

Summary of Guidelines From Other Groups

The Centers for Disease Control and Prevention (CDC), UK National Guidelines, American Academy of Family Physicians (AAFP), and the Society of Obstetricians and Gynaecologists of Canada (SOGC) do not recommend routine serologic screening for genital herpes in asymptomatic adults or adolescents.[51-53] The CDC guidelines note that type-specific HSV serologic screening for genital herpes may be helpful in the following situations: patients who present with recurrent atypical genital symptoms and HSV cultures are negative, when a clinical diagnosis of genital herpes is made without laboratory confirmation, and in people who have partners known to have genital herpes.[19,54] Finally, the CDC guidelines state that providers should consider serologic testing for genital herpes in persons presenting for an STD evaluation (especially for those persons with multiple sex partners), persons with HIV infection, and men who have sex with men at increased risk for HIV acquisition.[19,54]

For pregnant women, the AAFP recommends against routine serologic screening.[53] Both the CDC and SOGC recommend asking about a personal history of genital herpes.[51,54] The CDC, SOGC, and UK National Guidelines recommend conducting type-specific HSV serology for pregnant women who have had partners with known HSV to determine their risk of acquiring genital HSV in pregnancy.[51,52,54] However, CDC cautions that the effectiveness of antiviral therapy to decrease the risk for HSV transmission to pregnant women by infected partners has not been studied.[19,54] CDC recommends advising pregnant women not known to be HSV-2-infected to abstain from intercourse with partners known or suspected to have genital herpes during the third trimester of pregnancy; similarly, women not known to be HSV-1-infected should be advised to abstain from receptive orolabial intercourse with partners known or suspected of orolabial herpes infection.[19,54]

Recommendations for reducing neonatal HSV transmission focus on identifying active genital lesions or prodromal symptoms during the antenatal period. For those with active genital lesions (due to recurrent or primary infection) or prodromal symptoms that may indicate an impending outbreak, SOGC, the American Congress of Obstetricians and Gynecologists, CDC, and the National Collaborating Centre for Women's and Children's Health all recommend Cesarean delivery to reduce the risk of neonatal HSV infection.[51,54-56] The American Congress of Obstetricians and Gynecologists and SOGC recommend that women with active recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation to decrease the risk of clinical lesions and viral shedding at the time of delivery (and therefore decrease the need for Caesarean section).[51,55] Cesarean delivery is not recommended for women with a history of HSV infection but no active genital disease during labor.[55]

Current Clinical Practice in the United States

We were not able to find data on actual screening practices for genital herpes in the United States. Most guidelines described above do not recommend routine serologic screening for genital herpes in asymptomatic populations.

Chapter 2. Methods

Key Questions and Analytic Framework

The investigators, United States Preventive Services Task Force (USPSTF) members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope, Key Questions (KQs), and analytic framework (**Figure 1**) that guided our literature search and review.

In addition to our KQs, we also looked for evidence related to six Contextual Questions (CQs) focused on the prevalence, incidence and natural history of genital herpes in the United States. These CQs were not a part of our systematic review. They are intended to provide additional background information. Literature addressing these questions is summarized in Appendix A.

Data Sources and Searches

We searched PubMed/MEDLINE®, the Cochrane Library, and EMBASE for English-language articles published through March 31, 2016. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, screening tests, interventions, outcomes, and study designs. **Appendix B1** describes the complete search strategies. We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP). We retrieved all articles described in the 2005 review for the USPSTF[57] and evaluated them using our eligibility criteria. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. We will review all literature suggested by peer reviewers or public comment respondents and incorporate eligible studies into the final review. To minimize publication bias, we requested published or unpublished data on test accuracy (e.g., sensitivity, specificity) from studies comparing an available HSV-2 serologic test with the Western blot. We sent requests for data to all manufacturers currently listed with the FDA's Approved Device Registration and Listing Database[58] as being involved with the production or distribution of HSV-2 Enzyme-linked immunoabsorbent assays. We will review all information received from test manufacturers and incorporate eligible studies into the final review.

Study Selection

We developed inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs (**Appendix B2**).[59] We included English-language studies of immunocompetent adults or adolescents age 13 years or older, including pregnant women. For all KQs, studies of people who did not have symptoms or a clinical history of genital herpes were eligible, as were studies of asymptomatic partners of persons with known genital herpes (i.e., discordant couples). For KQ 1 (direct evidence that screening improves

health outcomes) we included only randomized controlled trials (RCTs) comparing groups that were screened with groups that were not screened.

For KQ 2 (screening test accuracy), we searched for studies that assessed the accuracy of FDA-approved serologic tests for HSV-2 (e.g., sensitivity, specificity) compared with the, Western blot. The Western blot has been used as a gold standard in studies assessing commercially available serologic tests in the United States. Eligible populations could be either symptomatic or asymptomatic (or a combination of both). We excluded studies using tests that were not serologic (e.g., viral culture), not type-specific, and not commercially available or FDA-approved. We included studies assessing "paired" tests (i.e., those reporting HSV-1 and HSV-2) but we did not assess the accuracy of HSV-1. Good-quality, recent (within 5 years) systematic reviews, as well as trials or observational studies published since the most recent review for the USPSTF were eligible for KQ 2.

For KQ 3 (harms of screening), we included studies assessing the harms of screening in populations that were clearly asymptomatic (i.e., no current symptoms) and with no prior diagnosis of genital herpes with or without a comparison group; eligible harms outcomes included labeling, anxiety, stigma, and others (**Appendix B**). Good-quality, recent (within 5 years) systematic reviews were eligible as well as trials and observational studies published since the most recent review for the USPSTF.

studies assessing benefits or harms of preventive medications for HSV-2 (KQs 4-6), RCTs comparing FDA-approved oral antiviral medications for the suppression of recurrent genital HSV (acyclovir, famciclovir, or valacyclovir) with placebo were eligible. RCTs of behavioral counseling interventions (e.g., education or counseling; partner notification; barrier protection, such as condom use, or combinations of these components) were also eligible for KQs 5-6. For studies assessing the harms of antiviral medications in pregnant women (KQ 6b), multi-institution antiviral medication pregnancy exposure registries were eligible. Eligible outcomes included reduced rates of symptomatic episodes of genital herpes and genital herpes transmission (including measures of HSV-2 seroconversion). For KQ 5b (effectiveness of interventions in pregnant women), eligible outcomes included rates of neonatal HSV infection and reduced rates of symptomatic genital herpes at delivery. For KQ 4 (effects of antiviral medication on subclinical HSV-2 shedding) we included any outcome measure of subclinical HSV-2 shedding (e.g., percentage of days with any shedding detected); however, we did not include measures of viral shedding during symptomatic occurrences. Eligible harms outcomes for intervention studies (KQ 6) included medication-related adverse event and harms of behavioral counseling interventions (e.g., psychosocial harms). We did not include outcome such as the transmission or acquisition of HIV. Other effective strategies of preventing HIV transmission exist,[60,61] and HIV prevention does not appear to be a strong rationale supporting screening for asymptomatic HSV-2 infection in U.S. primary care settings.

Two investigators independently reviewed titles and abstracts. We dually and independently reviewed the full text of abstracts marked for potential inclusion by either reviewer. Two experienced team members then resolved any disagreements.

Quality Assessment and Data Abstraction

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. A second investigator checked all data extractions for completeness and accuracy.

We assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B3**).[62] Two independent reviewers assigned quality ratings for each study. Disagreements were resolved by discussion with an experienced team member. We included only studies rated as having good or fair quality.

Data Synthesis and Analysis

We qualitatively synthesized findings for each key question by summarizing the characteristics and results of included studies in tabular and narrative format. To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of studies following established guidance.[63] We qualitatively assessed the populations, serologic tests, interventions, comparators, outcomes, and study designs, looking for similarities and differences.

For KQ 2 (the only KQ with sufficient numbers of studies addressing similar questions to conduct quantitative syntheses), we constructed two by two tables and calculated sensitivity and specificity and their 95 percent confidence intervals. When studies did not report sufficient data to populate a two by two table (e.g., number of true positive and false positive serologic test results) we calculated values based on the data provided (when possible). For each type of serologic test, we calculated pooled sensitivities and specificities using a hierarchical summary receiver-operator curve (HSROC) analysis when at least three similar studies were available. The HSROC simultaneously compares sensitivity and specificity (accounting for their correlation) for all studies comparing a particular serologic test with the Western blot. We conducted separate models for each type of serologic test and also conducted separate analyses for HerpeSelect® using the manufacturer recommended cutpoint for test positivity (1.1) and for higher cutpoints reported in the literature. We used the metandi program in Stata version 14[64] to conduct all quantitative analyses.

For each KQ, we assessed the consistency of results among studies (similar magnitude and direction of effect); precision of certainty surrounding an effect estimate; reporting bias; overall quality and limitations of the group of included studies; and applicability.

Expert Review and Public Comment

The draft report was reviewed by content experts, USPSTF members, and AHRQ Medical Officers, and was revised based on comments. This draft will also be posted for public comment; revisions will be made based on comments received.

USPSTF Involvement

This review was funded by AHRQ. Staff of AHRQ and members of the USPSTF participated in developing the scope of the work and reviewed draft manuscripts, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

We identified 3,068 unique titles and abstracts and assessed 281 full texts for eligibility (**Figure 2**). We excluded 261 articles for various reasons detailed in **Appendix C** and included 18 published studies of good or fair quality. Of the included studies, 11 were studies of HSV-2 serologic test accuracy (Key Question [KQ] 2), 2 assessed harms of screening for asymptomatic HSV-2 infection (KQ 3), and 4 were randomized controlled trials (RCTs) focused on the benefits of oral antiviral medications (KQs 4,5) one of which also reported on harms (KQ 6). We identified no eligible studies for KQ 1 (direct evidence of screening). Details of quality assessments of included studies and studies excluded because of poor quality are provided in **Appendix D**.

Results by Key Question

Key Question 1. Direct Evidence That Serologic Screening for Genital HSV-2 Infection Improves Health Outcomes

We found no eligible studies that addressed this question.

Key Question 2. Accuracy of Serologic Screening Tests for Detecting HSV-2 Infection

We included 11 good- or fair-quality studies assessing the accuracy of one or more type-specific HSV-2 serologic tests compared with the Western blot (**Table 2**).[65-75] All 11 studies enrolled adults and none enrolled pregnant women; two studies enrolled participants as young as 15 years of age, but neither described the proportion of participants who were less than 18 years of age (or reported outcomes separately).[66,72,76] Four of the 11 included studies described the age of participants: in those, mean or median age ranged from 25 to 35 years.[65,67,69,75] Two studies enrolled only women,[66,75] and one enrolled only men;[74] of the 8 other studies, one enrolled a minority of women (33%),[67] one enrolled a majority of women (64%),[77] and 6 did not describe the sex of participants. Most studies did not report on race or ethnicity; 2 studies set in the United States enrolled participants that were 23 to 31 percent non-white.[69,77] Most studies (k=8) enrolled a population with HSV-2 prevalence greater than 40 percent based on Western blot (range 41-70%).

Two of the 11 included studies described whether enrolled participants had current or prior symptoms consistent with genital herpes.[69,77] One enrolled U.S. college students with no current or previous symptoms consistent with genital herpes[77]and the other study enrolled men seeking care at U.S. sexually transmitted infection (STI) clinics, 35 percent of whom had symptoms of a STI (17% were later diagnosed with genital herpes).[69] In all other studies, the proportion of participants who had current or past symptoms consistent with genital herpes was not described.

Few studies described the prevalence of other current or past STIs; 2 studies reported on the prevalence of HIV (12%[73] and 52%[75]) and one study reported on the percentage of participants with various STIs (35% had symptoms of a STI).[69] Five studies reported on the seroprevalence of HSV-1; in 4 studies, the seroprevalence ranged from 56 to 99 percent[66,69-71] and in one U.S. study enrolling university students the seroprevalence of HSV-1 was very low (3.4% determined by Western blot).[77]

Most studies enrolled participants from one or more African countries; 3 were set in the United States,[65,69,70] and one enrolled participants from multiple countries (Argentina, Costa Rica, Korea, Mexico, Nigeria, Thailand, and Vietnam)[66] Study participants were selected from heterogeneous sources. Most studies assessed the accuracy of a serologic test in populations that were enrolled (or screened for enrollment) in other studies focused on STI, such as studies of HSV seroprevalence[66,73] and the seroprevalence or prevention of HIV.[67,68,71,72] Other studies enrolled participants from clinical settings (one from an STI clinic[69] and one from family planning clinics[75]) or from community settings (one enrolled male fishermen employed along the beaches of Lake Victoria[74] and one enrolled students from one U.S. university via flyers, online posts, and newspaper advertisements[77]).

Sample sizes ranged from 98 to 3,209. All 11 studies compared the Focus HerpeSelect® HSV-2 enzyme-linked immunosorbent assay (ELISA) with the Western blot. All studies used a test cutpoint value of 1.1 to define a positive test result (current manufacturer's cutpoint). Seven studies also assessed higher test cutpoints to boost specificity (ranging from 2.1 to 3.5).[66-68,71,73-75] Four studies also assessed the accuracy of the Biokit HSV-2 Rapid Test.[70,72-74]

HerpeSelect

Manufacturer's Recommended Cutpoint (1.1)

Ten studies (n=6,537 participants analyzed) provided sufficient data to estimate sensitivity and specificity of HerpeSelect using a cut point of 1.1;[65-68,70-75] The pooled estimates of sensitivity and specificity were 99 percent (95% CI, 97 to 100) and 83 percent (95% CI, 72 to 90), respectively; the positive and negative LRs were 6 (95% CI, 3 to 10) and 0.01 (95% CI, 0.004 to 0.04), respectively (**Table 3**). **Appendix E Figure 1** shows the hierarchical summary receiver-operator curve (HSROC) with 95 percent confidence ellipse using pairs of sensitivity and specificity. Results of individual studies are summarized in **Appendix E Table 1**.

Estimates for specificity were highly variable, ranging from 41 to 94 percent. Specificity ranged from 41 to 70 percent in 4 studies[68,73-75] from 80 to 89 percent in 3 studies;[66,67,71] and from 93 to 94 percent in 3 studies.[65,70,72] Of the 3 studies reporting a higher specificity (93 to 94%), 2 were conducted in the United States.[65,70]

Studies handled equivocal (or indeterminate) test results in various ways which may contribute to heterogeneity in estimates of test accuracy (**Appendix E Table 1**). Of the 10 studies reporting sensitivity or specificity, 5 excluded equivocal Western blot results,[66,67,70,73,74] 6 excluded indeterminate HerpeSelect® results,[65,66,68,70,71,74] and 3 excluded both equivocal Western blot and HerpeSelect® results.[66,70,74] Two studies did not describe the handling of equivocal test

results.[72,75]

Five studies reported a positive predictive value (PPV) using the manufacturer's cutpoint; estimates ranged from 37.5 to 86.0.[65,66,69,70,74] The lowest PPV was reported in a study enrolling U.S. university students (n=89) with no current or prior symptoms consistent with genital herpes (PPV 37.5; 95% CI, 10.2 to 74.1).[65] Estimates from the 4 other studies ranged from 77.4 to 86.0; of these, 2 enrolled populations outside the United States (one was set in Kenya,[74] and the other included participants from Argentina, Nigeria, Thailand Vietnam, and other countries;[66]) and 2 enrolled populations in the United States who had either sought testing specifically for HSV[69,70] or were considered to have a higher risk of infection for other reasons (men who have sex with men screened for enrollment in an HIV prevention trial).[70] Four studies reported negative predictive values (NPV); estimates ranged from 96 to 100.[65,66,70,74]

Higher Cutpoints

Seven studies (n=5,517 participants analyzed) also assessed higher cut points for a positive test than those recommended by the manufacturer (ranging from 2.2 to 3.5); all of these were set in Africa.[66-68,71,73-75] In general, estimates of specificity were higher at cut-points greater than 2.2, but estimates were still imprecise (**Table 3**). The joint estimates of sensitivity and specificity were 96 percent (95% CI, 94 to 97) and 89 percent (95% CI, 80 to 94), respectively; the positive and negative LRs were 8 (95% CI, 5 to 14) and 0.05 (95% CI, 0.04 to 0.71), respectively (**Table 3**). **Appendix E Figure 2** shows the HSROC with 95 percent confidence ellipse using pairs of sensitivity and specificity. Results of individual studies are summarized in **Appendix E Table 1**; as noted above, studies often excluded indeterminate test results from analyses.

Three studies reported PPV using cutpoints higher than the manufacturer's, estimates ranged from 86 to 98;[66,69,74] and two studies reported NPV using cutpoints higher than the manufacturer's, estimates ranged from 96 to 98 (**Appendix E Table 1**).[66,74]

Biokit HSV-2 Rapid Test

Four fair-quality studies (n= 1,512 participants analyzed) reported on the sensitivity and specificity of the Biokit HSV-2 Rapid Test; one was set in the United States,[70] 2 were set in African countries (Uganda[73] and Kenya[74]), and one was multinational.[72]The joint estimates of sensitivity and specificity were 84 percent (95% CI, 73 to 91) and 95 percent (95% CI, 93 to 97), respectively (**Table 3**). The positive and negative LRs were 17 (95% CI, 10 to 29) and 0.17 (95% CI, 0.09 to 0.30). **Appendix E Figure 3** shows the HSROC with 95 percent confidence ellipse using pairs of sensitivity and specificity. Results of individual studies are summarized in **Appendix E Table 2**.

Two studies reported PPVs of 92 and 95, and NPVs of 62 and 98, respectively.[70,74]

Key Question 3. Harms of Screening for Asymptomatic HSV-2

Characteristics and outcomes of the 2 included fair-quality studies are shown in **Appendix E Table 3**. The 2 studies enrolled different populations and measured different outcomes.[78,79] One

was included in the 2005 review for the USPSTF[78] and one was published after that review. Both studies were set in the United States and assessed the effect of a positive HSV-2 serologic test on psychosocial outcomes among people who reported no prior history of genital herpes.

One study was a qualitative assessment of the psychosocial effects of receiving a diagnosis of HSV-2 based on serological testing.[78] Investigators recruited 24 participants who reported no prior history of genital herpes and were found to be seropositive for HSV-2 (by Western blot). The mean age of participants was 35 and 58 percent were women. Participants were recruited from clinical settings (STI, maternal and infant care, family medicine, and research clinics) over a 10-month period; they completed an in-depth interview on their experience of receiving an HSV-2 diagnosis. The qualitative analysis identified 3 categories of themes: 1) short-term, emotional responses that included surprise, denial, confusion, distress, sadness, disappointment, and relief to know; 2) short-term, psychological responses that included fear of telling sex partners, anger at the source partner, guilt about acquiring or transmitting, and concern about transmitting to a child; and 3) perceived ongoing responses that included fear of telling future partners, concern about transmitting to a sex partner, feeling sexually undesirable, feeling socially stigmatized, feeling like "damaged goods," sex avoidance because of social responsibility, fear of transmitting to newborn child, and relationship concerns relating to the diagnosis. The authors concluded that participants exhibited strong emotional and psychological responses to their serological diagnoses of HSV-2, while observing that some of these responses were time limited.[78]

The second study enrolled individuals ages 14 to 30 years from an urban university setting and various clinical settings, including STI primary care, and adolescent clinics.[79] Of the 1,190 enrolled, 820 (68%) had serologic testing (type of test not described) and 149 (18%) were HSV-2 positive. Of those who screened positive for HSV-2, 93 (62%) returned for their initial test results and 33 participants returned for the 3-month follow-up. At 3 months, participants completed the herpes Health-Related Quality of Life (HRQOL) questionnaire, which addresses issues such as feelings of shame associated with herpes and feeling like herpes is "making life difficult."[80] Participants responded to each item using a 4-point scale that ranged from "very" to "not at all"; the total herpes HRQOL score was calculated by summing across items—a higher score indicated a better HRQOL and fewer problems with herpes. For individual item analysis, answers of "very" or "quite" were considered to be indicative of endorsing the experience.[79] A number of individual HRQOL items were endorsed frequently as "very" or "quite", including the following: "it is difficult to forget that I have herpes" (63%); "I worry about giving herpes to someone" (56%); "I worry about people finding out I have herpes" (48%); "I feel insecure about personal (intimate) relationships because of herpes" (30%); "I get depressed about having herpes" (30%); "I feel angry about having herpes" (30%); "I worry that people will reject me if they know I have herpes" (30%).[79] Items endorsed less frequently are shown in **Appendix E Table 3**.

Key Question 4. Effectiveness of Oral Antiviral Medications for Reducing Genital HSV-2 Viral Shedding

We included two fair-quality RCTs that reported on viral shedding outcomes.[81,82] Both were crossover RCTs comparing daily preventive antiviral medication with placebo over 6 to 8 weeks

in asymptomatic adults who screened positive for HSV-2 (**Tables 4 and 5**). One study did not describe how current or prior symptoms of genital herpes were ascertained;[82] the other study reported that participants had undergone HSV serologic testing as part of their clinical care, but had no current or prior symptoms that could be consistent with genital herpes (by self-report).[81]We identified no eligible studies enrolling pregnant women or adolescents.

One RCT (n=75) assessed valacyclovir 1 gram daily[81] and the other (n=66) assessed famciclovir 250mg twice daily.[82] Both enrolled populations who were predominantly female (≥ 64%) and had a minority of non-white participants (35%). The mean age of participants was 37 years (range 20 to 62 years) in one trial,[81] and the other trial enrolled participants with a median age of 38 (range 18 to 68 years).[82] Both were conducted at multiple centers in the United States. One recruited participants from various clinical settings (primary care clinics, gynecology practices, and STI clinics);[81] the other trial did not describe how participants were identified.[82] One RCT determined infection with HSV-2 via Western blot.[82] The other RCT used the commercially available HerpeSelect® ELISA to determine HSV-2 infection; positive samples with an index value between 1.1 and 3.5 were confirmed with a HSV-2 IgG inhibition assay.[81] Approximately half of participants in both trials also tested positive for HSV-1 infection (determined by the same methods as HSV-2 infection); only one trial described the number of participants with a clinical history of oral herpes (17%).[82]

One RCT reported a statistically significant reduction in viral shedding outcomes and the other did not. In the RCT comparing valacyclovir 1 gram daily with placebo, participants were educated on performing self-administered swabs of the anogenital area, which they completed once daily during the 60-day treatment period. Valacyclovir treatment significantly reduced subclinical days with HSV-2 shedding (1.5%) compared with placebo (5.1%, $p<0.001$), and also resulted in a greater proportion of subjects experiencing no days with shedding (84% vs. 54% respectively, $p=0.001$).[81] The RCT comparing famciclovir with placebo also collected daily swabs during the 60-day treatment period. Participants randomized to famciclovir and placebo had a similar risk of subclinical viral shedding; PCR samples were positive on 5.0 percent and 5.7 percent of subclinical days, respectively (RR, 0.8; 95% CI, 0.41 to 1.56; $p=0.52$).[82]

Key quality limitations across both trials included attrition (23% to 25% of participants) and unclear handling of missing data. In addition, the validity and reliability of daily self-swab to ascertain viral shedding is unclear, which contributes to potential measurement bias.

Key Question 5. Effectiveness of Preventive Medications and Counseling Interventions for Improving Health Outcomes

We included 4 fair-quality RCTs evaluating antiviral medications (**Table 4**).[76,81-83] Two focused on preventing transmission and enrolled adult heterosexual couples who were serologically discordant for HSV-2 infection (i.e., one partner had known genital herpes and the other partner had no prior diagnosis and was also seronegative for HSV-2);[76,83] and 2 enrolled asymptomatic adults with no prior history of genital herpes who were seropositive for HSV-2 infection.[81,82] We describe the characteristics and results of trials separately for adults with asymptomatic HSV-2 infection and discordant couples below. We identified no eligible studies that enrolled pregnant women or adolescents and no eligible studies that evaluated a behavioral counseling

intervention.

Asymptomatic Adults With HSV-2 Infection

Two crossover RCTs compared daily suppressive antiviral medication with placebo over 6 to 8 weeks (**Tables 4 and 5**); both also reported on viral shedding outcomes and study characteristics were described previously in the KQ 4 discussion. Both RCTs reported on the incidence of genital herpes symptoms; neither evaluated transmission of HSV-2 infection to a sexual partner.

In the RCT comparing valacyclovir 1 gram daily with placebo, participants were educated on the signs and symptoms of genital herpes and instructed to return to the clinic any time they suspected an outbreak of genital herpes. At 2 months, fewer participants in the valacyclovir group reported signs and symptoms of genital herpes than participants in the placebo group (12% vs. 23%, respectively); the authors report that the treatment effect was significant (p=0.033, controlling for the crossover effect), however the arithmetic mean of the difference between groups was not significant (11%; 95% CI, -0.6 to 22).[81] In the RCT comparing famciclovir 250 mg twice daily with placebo, the percentage of people reporting genital lesions in the famciclovir and placebo groups was similar at 6 weeks (17.5% and 17.2%, respectively, p-value not reported).[82]

Key quality limitations across both trials included attrition (23% to 25% of participants), unclear handling of missing data, and risk of measurement bias. Symptoms were ascertained by self-report (not using a validated questionnaire) over a relatively short duration (6 to 8 weeks). One study enrolled subjects who had HSV serologic testing as part of their clinical care (including some who were enrolled from STI clinics);[81] results may not be applicable to those who screen positive (but who are not seeking testing for HSV infection).

Discordant Couples

Two RCTs compared the benefit of daily suppressive antiviral medication with placebo for preventing the transmission of HSV-2 between heterosexual couples who are discordant for HSV-2 infection; one RCT measured outcomes at 8 months[76,83] and the other at 12 to 24 months (**Tables 4 and 5**).[84] One study enrolled immunocompetent subjects,[76,83] while the other RCT was a substudy of HIV-1-serodiscordant couples in which the HIV-1-negative partner was also susceptible to HSV-2.[84] One RCT (n=1484 couples) assessed valacyclovir 500 mg daily[76,83] and the other (n=937 couples) assessed acyclovir 400 mg daily; in both studies, antiviral medication was provided to the infected partner[84] In both studies, the HSV-2-infected partners were predominantly female (67% or more). One study reported that participants were 89 to 91 percent Caucasian,[76,83] and the other did not describe race or ethnicity.[84] The median age of participants was 34 to 35 years in one trial[76,83] and 31 in the other trial.[84] Both studies were conducted in multiple countries; one enrolled from 96 study sites in the United States, Canada, Europe, Latin America, and Australia,[76,83] and one was conducted in 7 sub-Saharan African countries.[84]

One RCT determined infection with HSV-2 using the HerpeSelect® HSV-2 ELISA; positive samples with an index value less than 3.5 were confirmed with the Western blot.[84] The other RCT enrolled couples if the source partner had recurrent genital herpes with fewer than 10

episodes per year and the susceptible partner had a negative HSV-2 Western blot.[76,83] Approximately 51 to 54 percent of participants in one trial tested positive for HSV-1 infection (determined by Western blot),[76,83] and the other trial reported that 93 percent or more of participants were infected with HSV-1;[84] neither described the number of participants with a clinical history of oral herpes. Both RCTs reported on the transmission of HSV-2 infection to a sexual partner.

In the RCT comparing valacyclovir with placebo, fewer HSV-2-susceptible partners in the valacyclovir group had symptomatic HSV-2 infection than partners randomized to placebo over 8 months (0.5% vs. 2.2%, respectively; hazard ratio: 0.25; 95% CI 0.08 to 0.75); similarly, few HSV-2-suceptible partners in the valacyclovir group seroconverted to HSV-2 than those in the placebo group (1.9% vs. 3.6%, respectively, p=0.04); hazard ratio: 0.52 (95% CI, 0.27 to 0.99).[76,83] In contrast, the RCT of HIV-1 serodiscordant couples conducted in sub-Saharan African countries that compared acyclovir with placebo did not find a reduction in transmission. For participants who tested negative for HSV-2 at enrollment and positive at study exit, samples collected at intervening quarterly visits were used to identify the time of HSV-2 seroconversion. At follow-up (median 18 months), the number of susceptible partners with seroconversions was not statistically different between the acyclovir group (40) and placebo group (28), which indicated seroincidence of 5.9 and 4.3 cases per 100 person-years, respectively (hazard ratio, 1.35; 95% CI, 0.83 to 2.20, p=0.22).[84]

Key limitations across both trials included high attrition; 22 percent of couples withdrew from one trial,[76,83] and the overall attrition was 66 percent in the other trial (partially accounted for by imputing missing data).[84]

Key Question 6. Harms of Preventive Medications and Behavioral Counseling Interventions

We included one fair-quality RCT enrolling asymptomatic adults with no known history of genital herpes who screened positive for HSV-2 infection.[81] This trial was also included in KQs 4 and 5; study characteristics are described in detail in KQ 4 and shown in **Table 4**. We identified no studies enrolling pregnant women and no trials assessing the benefits or harms of behavioral counseling interventions for asymptomatic adults who screen positive for HSV-2. Rates of reported adverse events were similar among groups randomized to valacyclovir and placebo, including dizziness, headache and nausea (**Appendix E Table 4**).[81]

Key Question 7. Association Between Subclinical Viral Shedding and Health Outcomes

We had insufficient evidence to establish the benefit of preventive medications for reducing genital HSV-2 subclinical viral shedding and therefore did not address this KQ.

Chapter 4. Discussion

Summary of Evidence

Table 6 provides a summary of findings in this evidence review. This table is organized by Key Question (KQ), then by population or screening test and provides a summary of outcomes along with our assessments of consistency, precision, quality, and applicability.

Evidence for Benefit and Harms of Screening for HSV-2 Infection

We did not identify any eligible studies directly assessing the benefits or harms of serologic screening for HSV-2 compared with no screening. Therefore, we reviewed literature that might establish an indirect chain of evidence from multiple questions that link screening to health outcomes (KQs 2 through 7).

We found evidence from two uncontrolled observational studies that detection of unexpected HSV-2 by screening is associated with potential psychosocial harms, including anxiety, worry, and distress from an HSV-2 diagnosis. Our conclusions about the potential harms of screening differ slightly from those of other reviews focused on the harms of HSV-2 serologic testing.[41,85] This may reflect differences in scope or eligibility criteria (or both). For example, we excluded studies enrolling people who were seeking care for genital symptoms or concerns about recent exposure to someone with genital herpes.[86,87] We also excluded studies that enrolled people with prior symptoms of HSV-2. When an assessment of current and prior symptom status was not reported, we contacted authors to confirm whether (and how) prior symptoms were assessed. We also excluded other studies from our evidence synthesis that were included in prior reviews due to methodological shortcomings (i.e., poor quality), such as high attrition (and no methods to address missing data) and high risk of selection bias.[77,88]

Other potential harms of serologic screening include false-positive test results that lead to psychosocial distress and costs of confirmatory testing. Currently, there is no widely available gold standard to confirm a positive HSV-2. A Western blot is available through the University of Washington Clinical Virology lab at a cost of about $207.[89] Use of the BiokitHSV-2 has been advocated as a confirmatory test for positive HSV-2 results detected via HerpeSelect.® Some commercially available HSV-2 serologic tests are "paired"—i.e., they report both HSV-1 and HSV-2 results. Positive results for HSV-1 may cause confusion given that the test cannot indicate the site of infection.

Accuracy of Serologic Screening Tests for HSV-2 Infection

Our pooled estimates of sensitivity and specificity for the commercially available HerpeSelect® found a sensitivity of 99 percent (95% CI, 97 to 100%; 7,510 participants) and a specificity of 83 percent (95% CI, 72 to 90%; 6,537 participants) at the manufacturer's cutpoint (1.1) compared with the Western blot. Estimates for specificity varied and were imprecise, without a clear explanation for the observed heterogeneity. Potential explanations for false-

positive serologic test results include cross-reactivity with HSV-1 (or other viruses), recent seroconversion, geographic variability in HSV-2 strain variants, and lab error. One potential explanation is cross-reactivity with HSV-1 infection. Of the six studies that described HSV-1 prevalence among enrolled participants, 4 studies had a HSV-1 prevalence ≥ 93 percent and found specificity estimates ranging from 52 to 89 percent.[66,71,74,75] Specificity estimates were higher at 93 and 94 percent in two studies with a lower HSV-1 prevalence (1% and 64%).[65,70]

At higher cutpoints, estimates of sensitivity and specificity from eight studies in Africa were still imprecise. Our pooled estimate of sensitivity was 95 percent (95% CI, 94 to 97%; 5,517 participants) and specificity was 89 percent (95% CI, 80 to 94%; 5,517 participants). Four of these studies assessed the accuracy of the BiokitHSV-2 serologic test; our pooled estimates of sensitivity was 84 percent (95% CI, 73 to 91%; 1,512 participants) and specificity was 95 percent (95% CI, 92 to 97%; 1,512 participants).

These estimates of the accuracy of serologic tests are generally applicable to populations with a higher prevalence of HSV-2 infection than general primary care populations in the United States. Eight studies assessing the accuracy of HerpeSelect® enrolled a population with HSV-2 prevalence greater than 40 percent based on Western blot (range 41 to 70%); one enrolled a population with a prevalence of 28 percent;[73] and one enrolled a population with a prevalence of 9 percent.[65] Use of HerpeSelect® in a population with lower prevalence, similar to that of U.S. adults, would greatly increase the number of false positive tests, even if specificity were unchanged. For example, in a population of 100,000 with a prevalence of asymptomatic HSV-2 of 50 percent (similar to the prevalence in included studies) with a test sensitivity of 99 percent and specificity of 85 percent, there would be 49,500 true positive test results and 8,500 false positive tests (positive predictive value [PPV] would be 85%).

If the prevalence instead were 16 percent (similar to the seroprevalence in the general U.S. adult population among people with unknown symptom status), the number of true positives would decrease to 15,840 and the number of false positive tests would increase to 14,280 (PPV = 53%). True positives would decrease further and false positives would increase further if the prevalence were less than 16 percent. The true prevalence of asymptomatic HSV-2 infection in the United Sates is unknown. Prevalence estimates rely on serologic test results and are not confirmed with the Western blot. Although the overall seroprevalence of HSV-2 was 16 percent in the most recent NHANES survey, 3.8 percent of participants reported having been diagnosed with genital herpes and data was not collected regarding whether participants had prior symptoms consistent with herpes.[23] Of those who were HSV-2 seropositive, 14 percent reported having been diagnosed with genital herpes.[23] It is unclear what proportion of participants with no prior diagnosis of genital herpes who were identified as being HSV-2 seropositive may have true infection that is asymptomatic (or unrecognized) versus a false positive serologic test result.

If sensitivity were unchanged, screening a lower prevalence population would reduce the number of false negative tests, although the negative predictive value would change little. It is possible, however, that the sensitivity of the screening tests could be lower in a lower prevalence population due to such factors as lower antibody levels, thus increasing the number of false negative tests per 1,000 people tested. The direction of these changes with prevalence would be similar regardless of which cutpoint were used.

Benefits and Harms of Preventive Interventions for Asymptomatic People Who Are HSV-2 Seropositive or for Discordant Couples

We found limited evidence evaluating preventive interventions for asymptomatic adults who screen positive for HSV-2. No studies enrolled pregnant women or adolescents, and no eligible studies assessed behavioral counseling interventions.

Two RCTs (with a total of 141 participants) assessed the benefit of preventive antiviral medications for reducing HSV-2 viral shedding and symptomatic occurrences among adults seropositive for HSV-2 who reported no prior symptoms consistent with genital herpes. Evidence from these two trials does not allow an accurate estimate of the benefit of preventive antiviral medications for improving health outcomes. The two trials differed in several ways. They assessed different medications (valacyclovir and acyclovir), recruited from different sources, and used different tests to establish HSV-2 infection. Both assessed outcomes over a short time (6 to 8 weeks) and relied on self-report to ascertain symptom occurrence. This duration is likely inadequate to evaluate whether antiviral medications reduce the incidence of symptoms among populations who have been asymptomatic. Results were inconsistent and imprecise; one trial found benefit for valacyclovir compared with placebo for reducing viral shedding and symptom occurrences[81] and the other found no statistically significant differences between groups.[82]

Similarly, the two trials assessing preventive antiviral medications for reducing HSV-2 transmission between discordant partners were heterogeneous and found inconsistent results. One enrolled immunocompetent couples from primarily industrialized countries,[76] while the other enrolled couples discordant for both HIV and HSV-2 from sub-Saharan Africa.[84] The studies assessed different medications (valacylovir and acyclovir) and over different durations (8 months and a median of 18 months). One trial found benefit for valacyclovir compared with placebo for reducing symptomatic HSV-2 infection and HSV-2 seroconversion in the susceptible partner; however, the magnitude of benefit is modest and results are imprecise.

One trial assessed harms of medications; adverse events were similar between groups randomized to valacyclovir and placebo.[81] Although few studies eligible for our review assessed harms of antiviral medications, other reviews have concluded that there are few harms in nonpregnant adults.[90]

Limitations of the Review

We required studies to compare a U.S. Food & Drug Administration-approved, currently available serologic screening test with Western blot. We did not include preventive interventions that are not FDA-approved and currently unavailable in the United States, such as studies of topical Tenofovir gel or HSV-2 vaccines. We did not evaluate other comparisons, such as a serologic test compared with a viral PCR swab or culture to diagnose genital herpes. We focused on studies comparing a serologic test with the Western blot and did not include studies that assessed the concordance between two commercially available serologic tests (i.e., without comparing them to a gold standard).

For benefits, we did not evaluate every possible outcome. For example, we did not evaluate whether interventions for asymptomatic HSV-2 infection in persons with HIV prevents transmission of HIV.

We also limited our assessment to studies enrolling people who had no current or prior symptoms. For people with frequent symptomatic recurrences of genital herpes (more than four episodes per year), antiviral medications have been shown to reduce the frequency of recurrences; however, the magnitude of effect is somewhat uncertain and the quality of evidence is low. A Cochrane review published in 2014 evaluated the efficacy of antiviral medications (acyclovir, famciclovir, and valacyclovir) to suppress genital herpes outbreaks in nonpregnant adults.[90] Twenty-two trials were included; the risk of bias was considered high for half of the studies and unclear for the other half. The authors concluded that there was low-quality evidence that the risk of having at least one clinical recurrence was reduced with acyclovir (nine parallel-group trials, n=2,049; RR, 0.48; 95% CI, 0.39 to 0.58), valacyclovir (four trials, n=1,788; RR, 0.41; 95% CI, 0.24 to 0.69), or famciclovir (two trials, n=732; pooled RR, 0.57; 95% CI, 0.50 to 0.64).[90] It is unclear whether these results would apply to people who have less frequent recurrences (or who are asymptomatic).

Future Research Needs

Randomized controlled trials enrolling people with no (or unrecognized) genital herpes symptoms that directly compare screening with no screening and assess health outcomes (i.e., trials that address KQ 1, the overarching question) over at least 12 months are required to improve the evidence base for serologic screening for HSV-2. Studies assessing the accuracy of HSV-2 serologic tests that enroll asymptomatic people from primary care settings in the United States would clarify the accuracy of these tests when used in the general population (related to our KQ 2). Such studies should aim to include a representative asymptomatic community population, to avoid spectrum bias, and compare all results with the Western blot. Future studies of serologic test accuracy should clearly describe the handling of indeterminate (or equivocal) test results.

To better understand the frequency and severity of the harms of screening, longitudinal studies with sensitive measures of psychosocial distress attributable to screening or to positive screening results are needed. These studies should evaluate pre- and post-test counseling approaches and should include such outcomes as disruption of relationships.

Future studies that assess the benefit of behavioral counseling interventions specifically focused on genital herpes (compared with no intervention) among asymptomatic populations that screen positive for HSV-2 would help clarify whether non-medication interventions are effective for improving health outcomes. Finally, RCTs assessing the effectiveness of antiviral medications for reducing viral shedding and improving health outcomes among persons with asymptomatic HSV-2 infection should enroll screen-detected populations and measure outcomes over a longer duration.

The net benefit of serologic screening for HSV-2 could be affected by development of an

effective vaccine. Previous clinical trials of HSV vaccines have not shown efficacy; however, work in this area is ongoing[91] and may prove to be an effective prevention strategy.

Conclusion

Serologic screening for HSV-2 infection is associated with psychological harms and false-positive test results, particularly in populations that have a low prevalence of HSV-2. Evidence on the benefit of preventive antiviral medications for reducing viral shedding or improving health outcomes (e.g., reducing symptom occurrences) in asymptomatic adults who screen positive for HSV-2 is uncertain. We found no evidence evaluating preventive interventions in pregnant women or adolescents.

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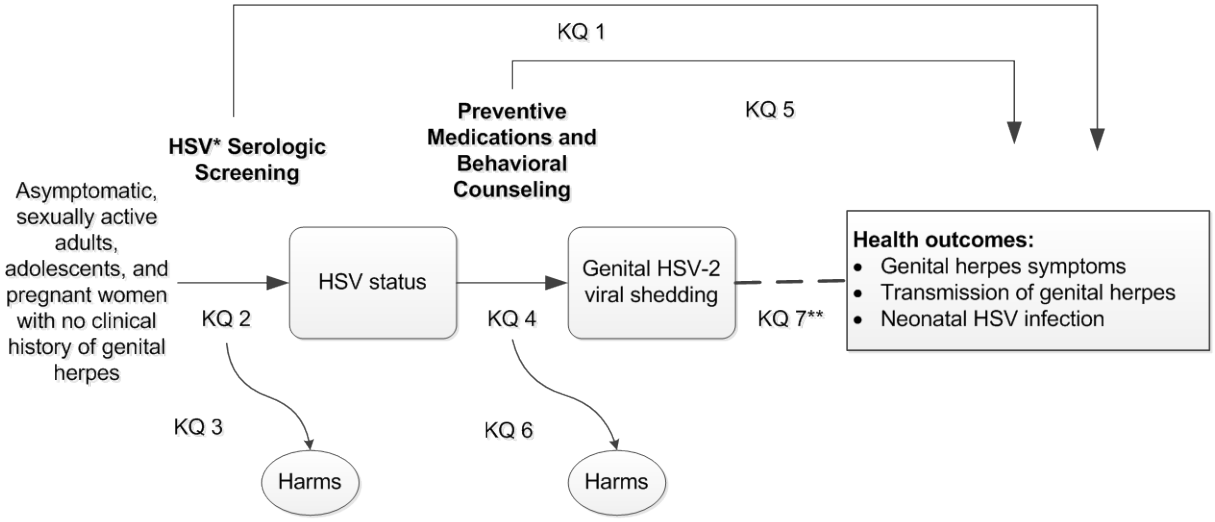
Figure 1. Analytic Framework and Key Questions



*Studies that screen using an HSV-2 serologic test alone or a "paired" (HSV-1 and HSV-2) serologic test will be included if they meet other eligibility criteria; however, only the accuracy of test characteristics related to HSV-2 serological tests will be evaluated.
**KQ 7 will only be addressed if there is insufficient literature for KQs 1 and 5 but sufficient literature for KQ 4.

Abbreviations: KQ=key question; HSV=herpes simplex virus.

Key Questions to Be Systematically Reviewed

1. a. Does serologic screening for herpes simplex virus type 2 (HSV-2) or combined testing for herpes simplex virus type 1 (HSV-1) and 2 in asymptomatic nonpregnant adults and adolescents reduce future symptomatic episodes and transmission of genital herpes?
   b. Does serologic screening for HSV-2 or combined testing for HSV-1 and HSV-2 in pregnant women reduce neonatal HSV infection and symptomatic episodes of genital herpes at delivery?
2. What is the accuracy of serologic screening for HSV-2 in asymptomatic adults, adolescents, and pregnant women?
3. a. What are the harms of serologic screening for HSV-2 or combined testing for HSV-1 and HSV-2 in asymptomatic nonpregnant adolescents and adults?
   b. What are the harms of serologic screening for HSV-2 or combined testing for HSV-1 and HSV-2 in asymptomatic pregnant women?
4. How effective are oral antiviral medications in reducing genital HSV-2 viral shedding in asymptomatic adolescents, adults, and pregnant women?
5. a. How effective are preventive medications and behavioral counseling interventions in reducing future symptomatic episodes and transmission of genital herpes in asymptomatic nonpregnant adults and adolescents?
   b. How effective are preventive medications and behavioral counseling interventions in reducing neonatal HSV infection and symptomatic episodes of genital herpes at delivery in pregnant women?
6. a. What are the harms of preventive medications and behavioral counseling interventions for reducing future symptomatic episodes and transmission of genital herpes in asymptomatic nonpregnant adults and adolescents?
   b. What are the harms of preventive medications and behavioral counseling interventions for reducing neonatal HSV infection and symptomatic episodes of genital herpes at delivery in asymptomatic pregnant women?
7. What is the evidence supporting an association between subclinical genital HSV-2 viral shedding and health outcomes in asymptomatic adults, adolescents, and pregnant women who are seropositive for HSV-2?

Contextual Questions

Contextual questions will not be systematically reviewed and are not shown in the Analytic Framework.

1. What proportion of asymptomatic adults, adolescents, and pregnant women who are identified as being seropositive for HSV-2, HSV-1, or both will have a recognized symptomatic episode of genital herpes?
2. Among asymptomatic adults, adolescents, and pregnant women who are identified as being seropositive for one virus subtype (HSV-1 or HSV-2), what proportion of recognized symptomatic episodes is due to a new (incident) HSV infection with a different subtype (i.e., nonprimary infection) versus a recurrent infection?
3. What is the estimated incidence rate of neonatal HSV infection in the United States?
4. What proportion of neonatal HSV infections in the United States is attributed to HSV-1 and HSV-2?
5. Are externally validated, reliable risk stratification tools available that distinguish persons who are more or less likely to have genital herpes?
6. What populations are at higher risk for genital herpes infection?

Figure 2. Summary of Evidence Search and Selection

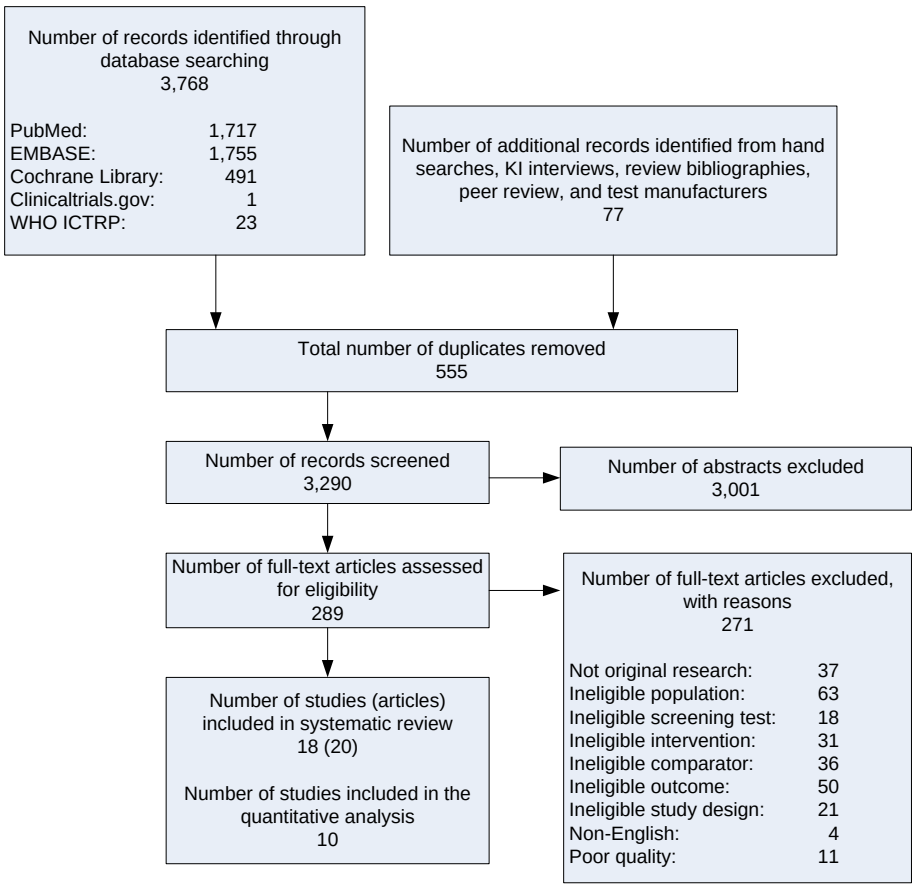


Table 1. Clinical Categories of Genital HSV Infection[92]

Category	Definition	Clinical Manifestations
Primary genital HSV infection	Newly acquired genital HSV infection (either HSV-1 or HSV-2); no serum antibody is present when symptoms appear	Painful genital ulcers or vesicular lesions, potentially associated with dysuria, fever, tender local inguinal lymphadenopathy, and headache; can be subclinical or entirely asymptomatic
Nonprimary genital HSV infection	Newly acquired genital infection with HSV-2 (or HSV-1) in an individual previously seropositive to the other subtype. Type-specific antibody to one subtype is initially present while antibody to the new infection may take weeks or months to appear	In general, manifestations tend to be milder than those of primary infection (e.g., fewer lesions and less systemic symptoms); can be subclinical or entirely asymptomatic
Recurrent genital HSV infection	Reactivation of genital HSV in which the HSV type recovered from a lesion is the same type as antibodies in the serum; can be the first clinical episode in people with prior asymptomatic (or unrecognized) genital HSV infection	Ulcerative or vesicular lesions sometimes associated with a prodrome of local itching, tingling, or pain; usually milder and shorter in duration than primary infection; can be subclinical or entirely asymptomatic
Asymptomatic genital HSV infection	Genital HSV infection in which serum antibody is present, but there is no known history of clinical outbreaks	None or potentially mild or unrecognized symptoms previously attributed to another cause

Abbreviations: HSV = herpes simplex virus.

Table 2. Characteristics of Included Studies Assessing the Accuracy of Serologic Screening Tests for HSV-2 (Key Question 2)

Author, Year Study Design Quality	Eligible Serologic Test(s)	Population (N)	Recruitment Setting; Country	Age, Mean (SD)	% Female	% Non-White	% with Comorbid STI	% HSV-1 Positive (Test)[1]
Ashley-Morrow, 2004[66] Cross-sectional Fair	HerpeSelect®	Women aged ≥15 years participating in a HSV seroprevalence study (675)	Study participants; Multinational[2]	NR	100	NR	NR	93-99 (WB)
Delany-Moretlwe, 2009[75] Cross-sectional Fair	HerpeSelect®	Adult women with unknown HSV-2 serostatus (98)	Family planning clinics; South Africa	26 (range 18-46 y)	100	NR	HIV-1: 52	NR
Golden, 2005[69] Cross-sectional Fair	HerpeSelect®	Men who had been tested for HSV at a STI clinic between 2001-2002 (108)	2 county STI clinics United States	Median: 35 (range 18-73 y)	0	23	1	56 (WB)
Hogrefe, 2002[71] Cross-sectional Fair	HerpeSelect®	Adults, varied by location: Kenya—women enrolled in a vitamin A study; Uganda (a) serologic samples from participants in a HIV seroprevalence study; Uganda (b) samples from HIV negative women; South Africa and Namibia—samples from healthy, primarily middle-income income individuals initially collected for HIV screening (785)	Varied by location; primarily study participants Multiple African countries[3]	NR	NR	NR	NR	89-100 (WB)
Lingappa, 2010[73] Cross-sectional Good	HerpeSelect® Biokit HSV-2	Adults participating in a study of genital herpes seroprevalence and incidence (493)	Study participants; Uganda	NR (see comments)	NR (see comments)	NR	HIV-1: 12	NR
Mark, 2007[65]; Mark, 2008 [77] Cohort study Good	HerpeSelect®	Urban university students with no history of genital herpes or genital sores who reported being sexually active within the past 6 months (100)	Recruited by flyers, announcement, and online/newspaper ad at 1 university United States	25 (4.4)	64	31%	NR	9 (HerpeSelect®); 3 (WB)

Table 2. Characteristics of Included Studies Assessing the Accuracy of Serologic Screening Tests for HSV-2 (Key Question 2)

Author, Year Study Design Quality	Eligible Serologic Test(s)	Population (N)	Recruitment Setting; Country	Age, Mean (SD)	% Female	% Non-White	% with Comorbid STI	% HSV-1 Positive (Test)[1]
Morrow, 2005[70] Cross-sectional Fair	HerpeSelect® Biokit HSV-2	2 populations enrolled: (1) adult MSM screened for enrollment in a clinical trial assessing acyclovir to reduce HIV transmission and (2) Consecutive serologic samples submitted for HSV WB testing (782)	Study participants and serologic samples sent to the University of Washington Virology lab during a 4-week period United States	NR	0	NR	NR	64 (WB)
Mujugira, 2011[67] Cross-sectional Good	HerpeSelect®	HIV-negative adult men and women participating in the Partners in Prevention HSV/HIV Transmission Study[4] (3408)	Study participants; Multiple African Countries[5]	Median: 34	33	NR	NR	NR
Ng'ayo, 2010[74] Cross-sectional Fair	HerpeSelect® Biokit HSV-2	Adult men who worked in the fishing industry who reported being sexually active in the previous 2 weeks (250)	Community (beaches along Lake Victoria); Kenya	NR (≥18 y eligible)	0	NR	NR	NR
Smith, 2009[68] Cross-sectional Fair	HerpeSelect®	Adult men who were HIV-negative participating in a trial to determine the effectiveness of circumcision in reducing HIV incidence(120)	Study participants (recruited from STI clinics, workplaces and community organizations) Kenya	NR	0	NR	NR	NR
Van Dyck, 2004[72] Cross-sectional Fair	HerpeSelect® BiokitHSV-2	Adults who were enrolled in a study on factors determining the spread of HIV (330)	Study participants Multiple African countries[6]	NR (≥15-49 y eligible)	NR	NR	NR	NR

[1] This is the test used to determine HSV-1 seropositivity.
[2] Argentina, Costa Rica, Korea, Mexico, Nigeria, Thailand, and Vietnam.
[3] Kenya, Uganda, South Africa, Namibia.
[4] This is a randomized trial of acyclovir (for HSV-2 suppressive therapy) to reduce HIV-1 transmission.
[5] Kenya, Rwanda, Tanzania, Uganda, Botswana, South Africa and Zambia.
[6] Kenya, Zambia, Benin, and Cameroon.

Abbreviations: HIV = human immunodeficiency virus; HSV = Herpes Simplex Virus; MSM = men who have sex with men; N= number; NR= not reported; SD= standard deviation; STI = sexually transmitted infection; WB= Western blot.

Table 3. Accuracy of Serologic Screening Tests for HSV-2 Compared With Western Blot[a]

Test (Cutpoint)	Studies, n	Sensitivity (95% CI), %	Specificity (95% CI), %	LR+ (95% CI)	LR− (95% CI)
HerpeSelect® (1.1)	10 (6,537)	99 (97 to 100)	83 (72 to 90)	6 (3 to 10)	0.01 (0.004 to 0.04)
HerpeSelect® (2.2 to 3.5)	7 (5,517)	96 (94 to 97)	89 (80 to 84)	8 (5 to 14)	0.05 (0.35 to 0.72)
BiokitHSV-2	4 (1,512)	84 (73 to 91)	95 (93 to 97)	17 (11 to 29)	0.16 (0.92 to 0.30)

[a] Values summarize our pooled estimates of sensitivity and specificity based on hierarchical summary receiver-operator curve and bivariate analyses

Table 4. Characteristics of Included Studies Assessing Antiviral Medications in Nonpregnant Adults (Key Questions 4 and 5)

Author, Year Study Design Quality	G1 (N) G1 (N)	Duration (Wks)	Population	Recruitment Setting; Country	HSV-2 test	Mean Age (SD)	% F	% Non-White	% HSV-1 Positive
Sperling, 2008[81] RCT (crossover) Fair	Total (63) Valacyclovir 1g daily first (36) Placebo first (37)	8 active; 8 placebo	Adults ≥ 18 seropositive for HSV-2 with no active lesions or symptoms consistent with genital herpes and no history of recurrent or undiagnosed symptoms consistent with genital herpes	13 clinical settings[a] (STI clinics, primary care clinics, and gynecology practices) United States	HerpeSelect®[b]	37 (NR)	75	35	56-57
Leone, 2007[82] RCT (crossover) Fair	Total (66) Famciclovir 250 mg twice daily first (NR) Placebo first (NR)	6 active; 6 placebo	Adults ≥ 18 seropositive for HSV-2 with no history of symptomatic genital herpes	7 centers (not otherwise specified) United States	Western blot	Median (range): 38 (18-68)	64	35	55
Corey, 2004[76] Kim, 2008[83] RCT (parallel) Fair	Total (1484 couples) Valacyclovir 500mg once daily (743 couples) Placebo (741 couples)	32	Adult ≥ 18 HSV-2 serodiscordant heterosexual couples	96 study sites (not otherwise specified) United States, Canada, Europe, Latin America, and Australia	Western blot	Median: 34-34 (range, 18-76)	33	10-11	70
Mujugira[84] RCT (parallel) Fair	Total (937 couples) Acyclovir 400mg twice daily (458 couples) Placebo (453 couples)	96	HSV-2 serodiscordant heterosexual couples enrolled into the Partners in Prevention HSV/HIV Transmission study[38]; couples were also serodiscordant for HIV (HSV-2 infected partners were also infected with HIV)	14 study sites (not specified) Kenya, Rwanda, Tanzania, Uganda, Botswana, South Africa, Zambia	HerpeSelect®[c]	Median: 31 (IQR 27-38)	12	NR	≥99

[a] Participants had either undergone specific HSV serologic testing as part of their clinical care or in response to local advertisements offering free HSV serologic testing.
[b] Samples with an index value of 1.1 to 3.5 were confirmed with HSV-2 IgG inhibition assay to eliminate false-positive test results.
[c] Samples with an index value of ≥3.5 were considered positive to improve test specificity, and confirmed by Western blot.

Abbreviations: F= female; G = Group; HSV= herpes simplex virus; IQR= Interquartile range; mg= milligrams; N= number; NR= not reported; wks= weeks; RCT= randomized controlled trials; SD= standard deviation.

Table 5. Results of Included Studies Assessing Preventive Interventions (Key Questions 4 and 5)

Author, Year Study Design	G1 (N) G2 (N)	Dur, Wks	Viral Shedding Outcome Measure, Results	Symptomatic Episodes Outcome Measure, Results	HSV-2 Transmission Outcome Measure, Results
Sperling, 2008[81] RCT (crossover)	Total (63) Valacyclovir 1g daily first (36) Placebo first (37)	8 active; 8 placebo	Subjects with no shedding, N (%) G1: 47 (84) G2: 30 (54) p<0.001 % of days with any subclinical viral shedding, mean (SD) [a]G1: 1.5 (5.3) G2: 5.1 (9) [b]p<0.001	Subjects reporting no signs or symptoms of genital herpes, N (%): G1: 49 (88) G2: 43 (77) p=0.033	NR
Leone, 2007[82] RCT (crossover)	Total (66) Famciclovir 250 mg twice daily first (NR) Placebo first (NR)	6 active; 6 placebo	Subjects with any shedding, N (%) G1: 27 (42.9) G2: 29 (50.0) P=NR Reduction in subclinical shedding risk, G1 vs. G2: RR: 0.80 (95% CI, 0.41 to 1.56); p=0.52	Subjects reporting genital lesions, N (%): G1: 11 (17.5) G2: 10 (17.2) p=NR	NR
Corey, 2004[76] Kim, 2008[83] RCT (parallel)	Total (1484 couples) Valacyclovir 500 mg once daily (743 couples) Placebo (741 couples)	32	NR	NR	HSV-2 seroconversions, N (%) G1: 14 (1.9) G2: 27 (3.6) HR: 0.52 (95% CI: 0.27-0.99) p=0.04 Incidence of symptomatic genital herpes, N (%) G1: 4 (0.5) G2: 16 (2.2) HR: 0.25 (95%CI: 0.08-0.75) p=0.008

Table 5. Results of Included Studies Assessing Preventive Interventions (Key Questions 4 and 5)

Author, Year Study Design	G1 (N) G2 (N)	Dur, Wks	Viral Shedding Outcome Measure, Results	Symptomatic Episodes Outcome Measure, Results	HSV-2 Transmission Outcome Measure, Results
Mujugira[84] RCT (parallel)	Total (937 couples) Acyclovir 400 mg twice daily (458 couples) Placebo (453 couples)	288	NR	NR	HSV-2 seroconversions (N) G1: 40 G2: 28 HSV-2 incidence HR: 1.35 (95%CI: 0.83-2.20) p=0.220

[a] Persons with at least one swab during each crossover period.
[b] Nonparametric crossover analysis methods in the ITTC population (ITTC= intention to treat crossover, all subjects who had at least one dose of medication and 1 PCR result in each treatment period)

Abbreviations: g= gram; G = Group; NR = not reported; CND = cannot determine; RCT = randomized controlled trial; CI= confidence interval; HSV-2= Herpes Virus Simplex type 2; N= number; HR=hazard ratio

Table 6. Summary of Evidence

KQ	Population	No. of Studies (Total N) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
1	-	No studies identified	-	-	-	-	-	-	-
2	Adults without current symptoms of genital herpes	HerpeSelect® Cutpoint 1.1: 10 (6,537) Cutpoint 2.2 to 3.5: 7 (5,517) BiokitHSV-2: 4 (1, 512) Cross-sectional	HerpeSelect Cutpoint 1.1: Sens: 99 (95% CI 97 to 100) Spec: 83 (95% CI 72 to 90) HerpeSelect Cutpoint 2.2 to 3.5: Sens: 96 (95% CI 94 to 97) Spec: 89 (95% CI 80 to 94) BiokitHSV-2: Sens: 84 (95% CI 73 to 91) Spec: 95 (95% CI 93 to 97)	Herpeselect (any cutpoint): consistent/ imprecise BiokitHSV-2: consistent/ imprecise	Yes[a]	Fair	Most studies excluded equivocal test results from calculations of sensitivity/ specificity (or did not describe the handling of missing data); sampling strategy was often not adequately described	Moderate	Populations from African countries that have a high prevalence of HSV-2 infection (>50%); applicability to asymptomatic populations receiving care in U.S. primary care settings is limited
3	Asymptomatic adults with HSV-2 infection	2 (57) Qualitative study; Cohort study	Qualitative study: new HSV-2 diagnosis is associated with: 1) short-term, emotional responses (e.g., distress, sadness); 2) short-term, psychological responses (e.g., fear of telling sex partners); and 3) perceived ongoing responses (e.g., feeling sexually undesirable) Cohort study: individual items frequently reported as interfering in daily life on the herpes HRQOLQ: “It is difficult to forget I have herpes” (63%); “I worry about giving herpes to	Consistent/ imprecise	Not detected	Fair	Studies are uncontrolled (no concurrent control group of people who were not screened); due to study design and outcome measures, we cannot estimate a magnitude of effect or assess precision.	Low	Asymptomatic persons with no known history of genital herpes

Table 6. Summary of Evidence

KQ	Population	No. of Studies (Total N) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
			someone" (56%); "I worry about people finding out I have herpes" (48%); and others.						
4	Asymptomatic adults with HSV-2 infection	2 (141) crossover RCTs	Subclinical days with any genital HSV-2 viral shedding detected over 6-8 weeks: • Valacyclovir 1 g daily vs. placebo: 1.5% vs. 5.1%, respectively, p<0.001 • Famciclovir 250 mg twice daily vs. placebo: 5.7% vs. 5.0%, respectively; RR: 8.0; (95% CI, 0.41 to 1.56); p=0.52	Inconsistent/ imprecise	Not detected	Fair	Studies assessed different medications over a short duration; sample sizes were small and overall attrition was >20% in both trials	Insufficient	Asymptomatic adults with HSV-2 infection diagnosed (or confirmed by) Western blot.
5	Asymptomatic adults with HSV-2 infection	2 (141) crossover RCTs	Incidence of self-reported genital herpes symptoms at 6-8 weeks: • Valacyclovir 1 g daily vs. placebo: 12% vs. 23%, respectively, p=0.033 • Famciclovir vs. placebo: 17.5% vs. 17.2%, respectively (p-value NR)	Inconsistent/ imprecise	Not detected	Fair	Incidence was self-reported; outcomes were measured over a relatively short duration; samples sizes were small and overall attrition was >20% in both trials	Insufficient	Asymptomatic adults with HSV-2 infection diagnosed (or confirmed by) Western blot.
5	Discordant couples	2 (2421) RCTs	Incidence of HSV-2 seroconversion: • Valacyclovir vs. placebo at 32 weeks: benefit in favor of valacyclovir, HR 0.52 (95% CI: 0.27-0.99); p=0.04	Inconsistent/ imprecise	Not detected	Fair	Two studies assessed different medications over different durations in populations that	Insufficient	Asymptomatic adults with known, ongoing exposure to genital herpes from a partner

Table 6. Summary of Evidence

KQ	Population	No. of Studies (Total N) Study Designs	Summary of Findings by Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence	Applicability
			• Acyclovir vs. placebo at 96 weeks: no difference between groups, HR 1.35 (95% CI: 0.83-2.20); p=0.220				were heterogeneous		
6	Asymptomatic adults with HSV-2 infection	1 (62) RCT	Incidence of self-reported adverse events were similar between groups (headache, nausea)	Unknown/ Imprecise	Not detected	Fair	Unclear if adverse events were prespecified.	Insufficient	Generally healthy asymptomatic nonpregnant adults

[a] We found evidence for only two FDA approved serologic tests for HSV-2. We did not identify studies assessing the accuracy of other FDA approved tests (compared to the Western blot).

Abbreviations: CI= confidence interval; HSV =herpes simplex virus; KQ= key question; N= number; NA= not applicable; NPV= negative predictive value; PPV= positive predictive value; RCT= randomized controlled trial; Sens = sensitivity; Spec= specificity

Contextual Questions

During the review process, we identified literature addressing the Contextual Questions (CQs) below. These CQs were not a part of our systematic review. They are intended to provide additional background information related to the prevalence, incidence, and natural history of genital herpes in the United States.

Contextual Question 1. What proportion of asymptomatic adults, adolescents, and pregnant women who are identified as being seropositive for HSV-2, HSV-1, or both will have a recognized symptomatic episode of genital herpes?

Evidence addressing CQ 1 is summarized in **Appendix A Table 1**. To address this question, we identified trials or prospective cohort studies enrolling asymptomatic adults, adolescents, or pregnant women who had serologic testing for HSV-2 but reported no prior history of genital herpes. We required studies to follow participants over time and report the incidence of symptoms consistent with genital herpes. We identified six relevant studies; all enrolled adults seropositive for HSV-2 and most determined (or confirmed) HSV-2 seropositivity using the Western blot. Two studies included participants who were tested for HSV-2 in a clinical setting for various reasons (e.g., women suspected of transmitting HSV-2 to a partner).[92,93] and the others recruited participants from both clinical and research settings in the context of recruitment or enrollment in clinical trials focused on genital herpes. All studies focused only on participants who were seropositive and did not follow participants who were seronegative for HSV-2 to ascertain the proportion of participants who seroconverted or developed genital symptoms over time.

Across all six studies, 16 to 87 percent of participants developed signs or symptoms of genital herpes over a follow-up duration of 5 months or less (**Appendix A Table 1**). Studies varied in how symptom occurrence was measured, which may explain some of the heterogeneity in the observed rate of symptom occurrence. Of note, all six studies delivered counseling about the clinical signs and symptoms of genital herpes to all participants, and instructed participants to return for a clinical exam if signs or symptoms occurred. The three studies with the highest incidence of symptom occurrence (52 to 82%) included detailed counseling sessions on genital herpes, including education on atypical symptoms (e.g., vulvar irritation);[11,92,94] two of which described showing participants photographs of genital herpes lesions.[11,94]

Contextual Question 2. Among asymptomatic adults, adolescents, and pregnant women who are identified as being seropositive for one virus subtype (HSV-1 or HSV-2), what proportion of recognized symptomatic episodes is due to a new (incident) HSV infection with a different subtype (i.e., nonprimary infection) versus a recurrent infection?

None of the studies above reporting on the incidence of symptoms among asymptomatic persons who test positive for HSV-2 reported on whether incident symptoms were attributable to HSV-1

versus HSV-2. We found no other studies addressing this CQ.

Contextual Question 3. What is the estimated incidence rate of neonatal HSV infection in the United States?

We found no recent (published in 2014 or later), multistate registry (or multi-institutional) study reporting on the incidence of HSV infection in the United States. Estimates of neonatal HSV incidence in the United States vary widely (1 out of every 3,200 to 10,000 live births), and rates are measured using heterogeneous methods.[16,42-44]

The most recent estimate is based on a clinical laboratory reporting system initiated in New York City in 2006.[45] Between April 2006 and September 2010, 76 cases were detected and the average incidence was estimated at 13.3 per100,000 live births (or 1 per 7,519 live births). The most recent multistate estimate comes from a study using a pediatric inpatient discharge database to identify cases of neonatal HSV infection in 2006.[42] The estimated incidence of neonatal HSV was 9.6 per 100,000 births (95% CI, 4.3 to 12.0). Incidence rates varied by geographic region and race but the differences were not statistically significant; however, rates were significantly higher among cases for which the expected primary payer was Medicaid (15.1 cases per 100,000 live births) compared with private insurance or managed health care (5.4 cases per 100,000 live births).[42]

Contextual Question 4. What proportion of neonatal HSV infections in the United States is attributed to HSV-1 and HSV-2?

We identified one study that described the proportion of neonatal HSV infection attributed to HSV-1 and HSV-2; this study used New York City neonatal surveillance data and is described above (in CQ 3).[45] Starting in 2006, clinical laboratories were required to report positive results for HSV on specimens from infants aged ≤60 days who were New York City residents, and health care providers were required to report diagnoses of neonatal HSV infection for the same age group, regardless of whether laboratory results confirmed infection. Between 2006 and 2010, New York City neonatal HSV surveillance detected 76 cases (estimated incidence of 13.3 per 100,000 live births). Most reported cases were laboratory confirmed (91%); 41 percent (28 cases) were HSV-1 and 39 percent (27 cases) were HSV-2 (20% of cases were not typed).[45]

Contextual Question 5. Are externally validated, reliable risk stratification tools available that distinguish persons who are more or less likely to have genital herpes?

We did not identify any externally validated, reliable risk stratification tools that distinguish persons who are more or less likely to have genital herpes.

Contextual Question 6. What populations are at higher risk for genital herpes infection?

To address this question, we identified studies reporting on the incidence or prevalence of genital herpes (or HSV-2 seropositivity) in in the United States based on demographic or other issues. We limited the search to multisite studies published in the past 5 years. We identified few studies assessing the prevalence or incidence of genital herpes. Most evidence comes from cross-sectional seroprevalence studies; none reported on the risk of demographic or behavioral factors based on a multivariate analysis.

Estimates of HSV-2 seroprevalence based on NHANES data from 2005 to 2010[19] vary by age, gender, race and ethnicity, and geographic region. Among people 14 to 19 years of age, HSV-2 seroprevalence is estimated to be 1.4 percent compared with 26.1 percent in people 40 to 49 years of age.[19] Women have a higher estimated prevalence than men (20.9% vs. 11.5%), which is attributed to anatomic factors predisposing women to be more susceptible to HSV-2 infection than men. Non-Hispanic Blacks have the highest estimated seroprevalence of HSV-2 infection (39.2%), which is three times that of non-Hispanic Whites (12.3%).[19]

Appendix A Table 1. Incidence of Symptomatic Episodes Among Asymptomatic Persons Identified as Seropositive for HSV-2

Author, Year Study Design	Population (N)	Ascertainment of Herpes-Related Symptoms and HSV-2 Infection Follow-Up Duration	Proportion With Incident Genital Herpes Symptoms
Langenberg, 1989[92] Cohort	Women recruited from an urban city-county hospital and GYN clinic who were identified as HSV-2 seropositive but reported no history of genital herpes (62)	Self-report; Western Blot 5 months	52% (32) developed symptomatic genital herpes
Leone, 2007[82] RCT US	Men and women identified as HSV-2 seropositive who reported no prior history of genital herpes enrolled in a trial assessing viral shedding (66)	Self-report; Western Blot 42 days	17.2% (11, during placebo treatment); 17.5% (12, during antiviral medication treatment)
Frenkel, 1993[93] Cohort US	Pregnant women recruited from 3 private OB practices (264)	Self-report; Western Blot NR (followed until delivery)	16%[b] (63)
Tronstein, 2011[94] Cohort US	Adult men and women study participants from the University of WA Virology Research Clinic[c] (88)	Self-report; Western Blot Median: 57 days (IQR 47-62)	68% (95% CI, 58% to 78%) (60)
Sperling, 2008[81] RCT US	Adult men and women from 13 centers in the US (various clinical settings) identified as HSV-2 seropositive who reported no current or past symptoms consistent with genital herpes enrolled in a trial assessing viral shedding (56)	Self-report; HerpeSelect® ELISA (index values 1.1 to 3.5 confirmed with HSV-2 IgG inhibition assay) 2 months	23% (13, overall)
Wald, 2000[11] Cohort US	Adults seropositive for HSV-2 with no history of genital herpes, recruited from either (1) a primary care clinic or (2) participants evaluated for entry into a HSV-2 vaccine trial unexpectedly found to be HSV-2 positive[a] (53)	Self-report; Western blot 3 months	87% (46) reported having either genital lesions or localized genital symptoms during followup.

[a] All subjects attended an individual standardized educational session on genital herpes that included reviewing photographs of herpetic lesions. Photographs of both typical lesions (e.g., blisters and on genital herpes ulcers) and atypical lesions (e.g., fissures) were shown, and the common symptoms (e.g., itching and tingling) were discussed.

[b] Fifty-six percent (N=24) of women recognized HSV lesions during the 3rd trimester; 16 women delivered their babies by cesarean section because of genital herpes.

[c] Participants were enrolled in prospective studies of the natural history of genital HSV infection.

Abbreviations: CI= confidence interval; GYN = gynecology; HSV= herpes simplex virus; IQR= interquartile range; N= number; NR= not reported; OB= obstetrics; WA = Washington.

Search Strategies

PubMed intervention/treatment search, 4/30/15

Search	Query	Items found
#1	Search "Herpes Genitalis"[Mesh] OR "genital herpes simplex" OR "Herpesvirus 2, Human"[Mesh] OR "HSV-2"[All Fields] OR HSV2[All Fields] OR Simplexvirus[Mesh] OR "genital herpes"[tiab] OR “Herpes Simplex”[Mesh:NoExp]	36678
#2	Search screen*	557339
#3	Search (("Polymerase Chain Reaction/methods"[Mesh] OR "Immunoenzyme Techniques"[Mesh] OR "Immunoassay/methods"[Mesh] OR "Antibodies, Viral/analysis"[Mesh] OR "Antibodies, Viral/blood"[Mesh] OR "Enzyme-Linked Immunosorbent Assay/methods"[Mesh] OR "Viral Envelope Proteins/diagnostic use"[Majr] OR "Viral Envelope Proteins/analysis"[Majr] OR "Viral Envelope Proteins/immunology"[Majr] OR "Serologic Tests/methods"[Majr] OR "Serologic Tests/standards"[Majr] OR "DNA, Viral/analysis"[Majr] OR "Reagent Kits, Diagnostic"[Majr]))	351976
#4	Search (#1 and (#2 or #3))	5545
#5	Search ((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	598487
#6	Search (#4 and #5)	104
#7	Search (#1 and #3)	4689
#8	Search (#1 and #3) Filters: Systematic Reviews	16
#9	Search (#7 and #5)	85
#10	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "comparative study"[pt] OR "Epidemiologic Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR “observational study” OR “observational studies” OR "cohort"[tw] OR "case control"[tw])	3274355
#11	Search (#7 and #10)	1335
#12	Search (#8 or #9 or #11)	1391
#13	Search (#12 not #6)	1306
#14	Search ("Herpes Simplex/diagnosis"[Majr] OR "Herpes Simplex/virology"[Mesh] OR "Herpesvirus 2, Human/immunology"[Majr] OR "Herpes Genitalis/diagnosis"[Majr] OR "Simplexvirus/immunology"[Majr] OR "Herpes Genitalis/virology"[Majr])	8482
#15	Search ("Herpes Simplex/diagnosis"[Majr] OR "Herpes Simplex/virology"[Mesh] OR "Herpesvirus 2, Human/immunology"[Majr] OR "Herpes Genitalis/diagnosis"[Majr] OR "Simplexvirus/immunology"[Majr] OR "Herpes Genitalis/virology"[Majr]) Filters: Systematic Reviews	50
#16	Search (#14 and #5)	147
#17	Search (#14 and #10)	1453
#18	Search (#15 or #16 or #17)	1577
#19	Search (#12 or #18)	2262
#20	Search (#19 not #6)	2176
#21	Search ((psychosocial AND test*) OR (emotional AND test*) OR (emotional AND impact) OR (diagnosis AND psychosocial) OR (screen* AND psychosocial) OR (test* AND impact) OR "Social Stigma"[Mesh] OR stigma[tiab] OR labeling[tiab] OR "Anxiety/etiology"[Majr] OR Stereotyping[Mesh])	269132
#22	Search (#1 and #21)	379
#23	Search (#1 and #21) Filters: Publication date from 2010/01/01[a]	77
#24	Search ("Virus Shedding"[Mesh] OR "viral shedding"[All Fields] OR "Disease	54661

Search	Query	Items found
	Transmission, Infectious"[Mesh])	
#25	Search (#1 and #24)	820
#26	Search (#25 and #5)	125
#27	Search ((acyclovir OR famciclovir OR valacyclovir) OR “Antiviral Agents”[Mesh:NoExp] OR “Antiviral Agents ”[Pharmacological Action] OR “suppressive treatment”[Title/Abstract] OR “suppressive therapy”[Title/Abstract] OR suppressive agent*[Title/Abstract] OR suppressive drug*[Title/Abstract] OR antiviral drug*[Title/Abstract] OR therapy[Title/Abstract] OR “antiviral treatment”[Title/Abstract] OR antiviral agent*[Title/Abstract])	1549825
#28	Search (#1 and #27)	12155
#29	Search ("Patient Education as Topic"[Mesh] OR "Patient Education Handout" [Publication Type] OR "patient education"[All Fields] OR Counseling[Mesh] OR "Secondary Prevention"[Mesh] OR "Disclosure"[Mesh] OR disclosure[All Fields] OR "Contact Tracing"[Mesh] OR "partner notification"[All Fields])	169152
#30	Search (#1 and #29)	322
#31	Search ("Contraception, Barrier"[Mesh] OR "barrier protection" OR "Condoms"[Mesh] OR "Condoms, Female"[Mesh] OR condom*)	18461
#32	Search (#1 and #31)	302
#33	Search (#28 or #30 or #32)	12555
#34	Search (#33 and #5)	589
#35	Search (#6 or #8 or #12 or #20 or #23 or #26 or #34)	2821
#36	Search (#6 or #8 or #12 or #20 or #23 or #26 or #34) Filters: Humans	2474
#37	Search (#6 or #8 or #12 or #20 or #23 or #26 or #34) Filters: Humans; Adolescent: 13-18 years	693
#38	Search (#6 or #8 or #12 or #20 or #23 or #26 or #34) Filters: Humans; Adolescent: 13-18 years; Adult: 19+ years	1523
#39	Search ("Pregnant Women"[Mesh] OR "Pregnancy"[Mesh] OR "Pregnancy Complications, Infectious"[Mesh:NoExp] OR "Pregnancy Outcome"[Mesh])	724894
#40	Search (#35 and #39)	215
#41	Search (#40 not #38)	77
#42	Search (#38 or #41)	1600
#43	Search (#38 or #41) Filters: English	1461
#44	Search (#42 not #43)	139

[a] Publication date limits only apply to systematic review publications for KQ3.”

PubMed intervention/treatment search, 3/31/16

Search	Query	Items found
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#2	Search screen*	598637
#3	Search ((("Polymerase Chain Reaction/methods"[Mesh] OR "Immunoenzyme Techniques"[Mesh] OR "Immunoassay/methods"[Mesh] OR "Antibodies, Viral/analysis"[Mesh] OR "Antibodies, Viral/blood"[Mesh] OR "Enzyme-Linked Immunosorbent Assay/methods"[Mesh] OR "Viral Envelope Proteins/diagnostic use"[Majr] OR "Viral Envelope Proteins/analysis"[Majr] OR "Viral Envelope Proteins/immunology"[Majr] OR "Serologic Tests/methods"[Majr] OR "Serologic Tests/standards"[Majr] OR "DNA, Viral/analysis"[Majr] OR "Reagent Kits, Diagnostic"[Majr]))))	362549
#4	Search (#1 and (#2 or #3))	5650

Appendix B1. Detailed Methods

Search	Query	Items found
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#6	Search (#4 and #5)	108
#7	Search (#1 and #3)	4758
#8	Search (#1 and #3) Sort by: PublicationDate Filters: Systematic Reviews	17
#9	Search (#7 and #5)	89
#10	Search (("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "comparative study"[pt] OR "Epidemiologic Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR “observational study” OR “observational studies” OR "cohort"[tw] OR "case control"[tw]))	3442776
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#12	Search (#8 or #9 or #11)	1419
#13	Search (#12 not #6)	1330
#14	Search (("Herpes Simplex/diagnosis"[Majr] OR "Herpes Simplex/virology"[Mesh] OR "Herpesvirus 2, Human/immunology"[Majr] OR "Herpes Genitalis/diagnosis"[Majr] OR "Simplexvirus/immunology"[Majr] OR "Herpes Genitalis/virology"[Majr]))	8703
#15	Search (("Herpes Simplex/diagnosis"[Majr] OR "Herpes Simplex/virology"[Mesh] OR "Herpesvirus 2, Human/immunology"[Majr] OR "Herpes Genitalis/diagnosis"[Majr] OR "Simplexvirus/immunology"[Majr] OR "Herpes Genitalis/virology"[Majr])) Sort by: PublicationDate Filters: Systematic Reviews	51
#16	Search (#14 and #5)	151
#17	Search (#14 and #10)	1490
#18	Search (#15 or #16 or #17)	1615
#19	Search (#12 or #18)	2313
#20	Search (#19 not #6)	2223
#21	Search (((psychosocial AND test*) OR (emotional AND test*) OR (emotional AND impact) OR (diagnosis AND psychosocial) OR (screen* AND psychosocial) OR (test* AND impact) OR "Social Stigma"[Mesh] OR stigma[tiab] OR labeling[tiab] OR "Anxiety/etiology"[Majr] OR Stereotyping[Mesh]))	289684
#22	Search (#1 and #21)	402
#23	Search (#1 and #21) Sort by: PublicationDate Filters: Publication date from 2015/02/28	19
#24	Search (("Virus Shedding"[Mesh] OR "viral shedding"[All Fields] OR "Disease Transmission, Infectious"[Mesh]))	57328
#25	Search (#1 and #24)	851
#26	Search (#25 and #5)	128
#27	Search (((acyclovir OR famciclovir OR valacyclovir) OR “Antiviral Agents”[Mesh:NoExp] OR “Antiviral Agents ”[Pharmacological Action] OR “suppressive treatment”[Title/Abstract] OR “suppressive therapy”[Title/Abstract] OR suppressive agent*[Title/Abstract] OR suppressive drug*[Title/Abstract] OR antiviral drug*[Title/Abstract] OR therapy[Title/Abstract] OR “antiviral treatment”[Title/Abstract] OR antiviral agent*[Title/Abstract]))	1757360
#28	Search (#1 and #27)	12495
#29	Search (("Patient Education as Topic"[Mesh] OR "Patient Education Handout" [Publication Type] OR "patient education"[All Fields] OR Counseling[Mesh] OR "Secondary Prevention"[Mesh] OR "Disclosure"[Mesh] OR disclosure[All Fields] OR "Contact Tracing"[Mesh] OR "partner notification"[All Fields]))	177556
#30	Search (#1 and #29)	327
#31	Search (("Contraception, Barrier"[Mesh] OR "barrier protection" OR "Condoms"[Mesh]	19583

Appendix B1. Detailed Methods

Search	Query	Items found
	OR "Condoms, Female"[Mesh] OR condom*))	
#32	Search (#1 and #31)	321
#33	Search (#28 or #30 or #32)	12917
#34	Search (#33 and #5)	606
#35	Search (#6 or #8 or #12 or #20 or #23 or #26 or #34)	2836
#36	Search (#6 or #8 or #12 or #20 or #23 or #26 or #34) Sort by: PublicationDate Filters: Humans	2505
#37	Search (#6 or #8 or #12 or #20 or #23 or #26 or #34) Sort by: PublicationDate Filters: Humans; Adolescent: 13-18 years	702
#38	Search (#6 or #8 or #12 or #20 or #23 or #26 or #34) Sort by: PublicationDate Filters: Humans; Adolescent: 13-18 years; Adult: 19+ years	1553
#39	Search (("Pregnant Women"[Mesh] OR "Pregnancy"[Mesh] OR "Pregnancy Complications, Infectious"[Mesh:NoExp] OR "Pregnancy Outcome"[Mesh]))	782129
#40	Search (#35 and #39)	218
#41	Search (#40 not #38)	79
#42	Search (#38 or #41)	1632
#43	Search (#38 or #41) Sort by: PublicationDate Filters: English	1494
#44	Search (#42 not #43)	138
#45	Search ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	42552
#46	Search (#43 and #45)	0
#47	Search (#44 and #45)	0
#48	Search (#38 or #41) Sort by: PublicationDate Filters: Publication date from 2015/02/28; English	35
#49	Search (#42 not #43) Sort by: PublicationDate Filters: Publication date from 2015/02/28	0

Cochrane search, 4-30-15

ID	Search	Hits
#1	[mh "Herpes Genitalis"] or "genital herpes simplex" or [mh "Herpesvirus 2, Human"] or "HSV-2" or HSV2 or [mh Simplexvirus] or "genital herpes" or [mh ^"Herpes Simplex"]	875
#2	screen*	31885
#3	[mh "Polymerase Chain Reaction"/MT] or [mh "Immunoenzyme Techniques"] or [mh Immunoassay/MT] or [mh "Antibodies, Viral"/AN] or [mh "Antibodies, Viral"/BL] or [mh "Enzyme-Linked Immunosorbent Assay"/MT] or [mh "Viral Envelope Proteins"/DU] or [mh "Viral Envelope Proteins"/AN] or [mh "Viral Envelope Proteins" [mj]/IM] or [mh "Serologic Tests" [mj]/MT] or [mh "Serologic Tests" [mj]/ST] or [mh "DNA, Viral" [mj]/AN] or [mh "Reagent Kits, Diagnostic" [mj]]	5172
#4	#1 and (#2 or #3)	126
#5	[mh "Herpes Simplex"/DI] or [mh "Herpes Simplex"/VI] or [mh "Herpesvirus 2, Human"/IM] or [mh "Herpes Genitalis"/DI] or [mh Simplexvirus/IM] or [mh "Herpes Genitalis"/VI]	158
#6	(psychosocial and test*) or (emotional and test*) or (emotional and impact) or (diagnosis and psychosocial) or (screen* and psychosocial) or (test* and impact) or [mh "Social Stigma"] or stigma or labeling or [mh Anxiety/ET] or [mh Stereotyping]	27129
#7	#1 and #6	79
#8	#1 and #6 Publication Year from 2010 to 2015 [a]	56
#9	[mh "Virus Shedding"] or "viral shedding" or [mh "Disease Transmission, Infectious"]	1114
#10	#1 and #9	134
#11	#1 and #9 in Trials	120
#12	(acyclovir or famciclovir or valacyclovir) or [mh ^"Antiviral Agents"] or "Antiviral Agents" or "antiviral agent" or "suppressive treatment" or "suppressive therapy" or "suppressive agent"	146699

Appendix B1. Detailed Methods

ID	Search	Hits
	or "suppressive agents" or "suppressive drug" or "suppressive drugs" or "antiviral drug" or "antiviral drugs" or therapy:ti or therapy:ab or "antiviral treatment"	
#13	#1 and #12	526
#14	[mh "Patient Education as Topic"] or [mh "Patient Education Handout"] or "patient education" or [mh Counseling] or [mh "Secondary Prevention"] or [mh Disclosure] or disclosure or [mh "Contact Tracing"] or "partner notification"	14041
#15	#1 and #14	23
#16	[mh "Contraception, Barrier"] or "barrier protection" or [mh Condoms] or [mh "Condoms, Female"] or condom*	1486
#17	#1 and #16	52
#18	#13 or #15 or #17	577
#19	#13 or #15 or #17 in Trials	512
#20	#4 or #5 or #8 or #11 or #19	663
#21	Adult*:ti,ab,kw or adolescen*:ti,ab,kw or teen:ti,ab,kw or teens:ti,ab,kw or teenage*:ti,ab,kw	378104
#22	#20 and #21	432
#23	[mh "Pregnant Women"] or [mh Pregnancy] or [mh ^"Pregnancy Complications, Infectious"] or [mh "Pregnancy Outcome"] or pregnan*	30774
#24	#20 and #23	86
#25	#22 or #24	476

[a] Publication date limits only apply to systematic review publications for KQ3

Cochrane search, 3-31-16

ID	Search	Hits
#1	[mh "Herpes Genitalis"] or "genital herpes simplex" or [mh "Herpesvirus 2, Human"] or "HSV-2" or HSV2 or [mh Simplexvirus] or "genital herpes" or [mh ^"Herpes Simplex"]	921
#2	screen*	36090
#3	[mh "Polymerase Chain Reaction"/MT] or [mh "Immunoenzyme Techniques"] or [mh Immunoassay/MT] or [mh "Antibodies, Viral"/AN] or [mh "Antibodies, Viral"/BL] or [mh "Enzyme-Linked Immunosorbent Assay"/MT] or [mh "Viral Envelope Proteins"/DU] or [mh "Viral Envelope Proteins"/AN] or [mh "Viral Envelope Proteins" [mj]/IM] or [mh "Serologic Tests" [mj]/MT] or [mh "Serologic Tests" [mj]/ST] or [mh "DNA, Viral" [mj]/AN] or [mh "Reagent Kits, Diagnostic" [mj]]	5813
#4	#1 and (#2 or #3)	140
#5	[mh "Herpes Simplex"/DI] or [mh "Herpes Simplex"/VI] or [mh "Herpesvirus 2, Human"/IM] or [mh "Herpes Genitalis"/DI] or [mh Simplexvirus/IM] or [mh "Herpes Genitalis"/VI]	167
#6	(psychosocial and test*) or (emotional and test*) or (emotional and impact) or (diagnosis and psychosocial) or (screen* and psychosocial) or (test* and impact) or [mh "Social Stigma"] or stigma or labeling or [mh Anxiety/ET] or [mh Stereotyping]	31245
#7	#1 and #6	88
#8	#1 and #6 Publication Year from 2015 to 2016	14
#9	[mh "Virus Shedding"] or "viral shedding" or [mh "Disease Transmission, Infectious"]	1207
#10	#1 and #9	138
#11	#1 and #9 in Trials	123
#12	(acyclovir or famciclovir or valacyclovir) or [mh ^"Antiviral Agents"] or "Antiviral Agents" or "antiviral agent" or "suppressive treatment" or "suppressive therapy" or "suppressive agent" or "suppressive agents" or "suppressive drug" or "suppressive drugs" or "antiviral drug" or "antiviral drugs" or therapy:ti or therapy:ab or "antiviral treatment"	163346
#13	#1 and #12	549
#14	[mh "Patient Education as Topic"] or [mh "Patient Education Handout"] or "patient education" or [mh Counseling] or [mh "Secondary Prevention"] or [mh Disclosure] or disclosure or [mh "Contact Tracing"] or "partner notification"	17887

ID	Search	Hits
#15	#1 and #14	46
#16	[mh "Contraception, Barrier"] or "barrier protection" or [mh Condoms] or [mh "Condoms, Female"] or condom*	1613
#17	#1 and #16	54
#18	#13 or #15 or #17	609
#19	#13 or #15 or #17 in Trials	543
#20	#4 or #5 or #8 or #11 or #19	688
#21	Adult*:ti,ab,kw or adolescen*:ti,ab,kw or teen:ti,ab,kw or teens:ti,ab,kw or teenage*:ti,ab,kw	420923
#22	#20 and #21	457
#23	[mh "Pregnant Women"] or [mh Pregnancy] or [mh ^"Pregnancy Complications, Infectious"] or [mh "Pregnancy Outcome"] or pregnan*	33976
#24	#20 and #23	79
#25	#22 or #24	493
#26	#22 or #24 Publication Year from 2015 to 2016	18

EMBASE Intervention Search, 5-1-15

No.
Query
Results
87
#46
#44 NOT #45
1,974
#45
#44 AND [english]/lim
2,061
#44
#37 OR #43
302
#43
#41 NOT #42
1,871
#42
#41 AND [medline]/lim
2,173
#41
#37 OR #40
165
#40
#39 NOT #37
305
#39
#35 AND #38
657,903
#38
'pregnant woman'/exp OR 'pregnancy'/exp OR 'pregnancy complication'/de OR 'pregnancy outcome'/exp
2,008
#37

#36 AND ([adolescent]/lim OR [adult]/lim)
4,574
#36
#6 OR #8 OR #12 OR #20 OR #23 OR #26 OR #34 AND [humans]/lim
6,651
#35
#6 OR #8 OR #12 OR #20 OR #23 OR #26 OR #34
1,000
#34
#33 AND #5
4,014
#33
#28 OR #30 OR #32
670
#32
#1 AND #31
22,987
#31
'barrier contraception'/exp OR 'barrier protection':ab,ti OR 'condom'/exp OR 'female condom'/exp OR condom*
871
#30
#1 AND #29
649,474
#29
'patient education'/exp OR 'patient education' OR 'counseling'/exp OR 'secondary prevention'/exp OR 'interpersonal communication'/exp OR disclosure OR 'contact examination'/exp OR 'partner notification'
2,624
#28
#1 AND #27
182,851
#27
acyclovir OR famciclovir OR valacyclovir OR 'antivirus agent'/de OR 'suppressive treatment':ab,ti OR 'suppressive therapy':ab,ti OR suppressive AND agent*:ab,ti OR suppressive AND drug*:ab,ti OR antiviral AND drug*:ab,ti OR therapy:ab,ti OR 'antiviral treatment':ab,ti OR antiviral AND agent*:ab,ti
786
#26
#25 AND #5
3,489
#25
#1 AND #24
185,507
#24
'virus shedding'/exp OR 'viral shedding' OR 'disease transmission'/exp
248
#23
#22 AND [2010-2015]/py [1]

[1] Publication date limits only apply to systematic review publications for KQ3

665
#22
#1 AND #21
363,258
#21
psychosocial AND test* OR (emotional AND test*) OR (emotional AND impact) OR (diagnosis AND psychosocial) OR (screen* AND psychosocial) OR (test* AND impact) OR 'social stigma'/exp OR 'stigma':ab,ti OR 'labeling':ab,ti OR 'anxiety'/exp/mj/dm_et OR 'stereotyping'/exp
2,054
#20
#19 NOT #6
4,827
#19
#12 OR #18
1,420
#18
#15 OR #16 OR #17
367
#17
#14 AND #10
1,171
#16
#14 AND #5
5
#15
#14 AND 'systematic review'/exp
3,962
#14
'herpes simplex'/exp/mj/dm_di OR ('herpes simplex'/exp/mj AND virology) AND 'herpes simplex virus 2'/exp/mj AND immunology OR 'genital herpes'/exp/mj/dm_di OR ('simplexvirus'/exp/mj AND immunology) OR ('genital herpes'/exp/mj AND virology)
1,081
#13
#12 NOT #6
3,832
#12
#8 OR #9 OR #11
1,682
#11
#7 AND #10
2,513,760
#10
'case control study'/exp OR 'cohort analysis'/exp OR 'epidemiological study' OR 'cross-sectional study'/exp OR 'organizational case study' OR 'crossover procedure'/exp OR 'seroepidemiologic study' OR 'epidemiology'/exp OR 'multicenter study'/exp OR 'multicenter study (topic)'/exp OR 'evaluation research'/exp
2,751
#9
#7 AND #5
24

#8
#7 AND 'systematic review'/exp
10,322
#7
#1 AND #3
3,317
#6
#4 AND #5
4,870,361
#5
'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR ('control':ab,ti OR 'controlled':ab,ti AND 'trial':ab,ti)
12,548
#4
#1 AND (#2 OR #3)
813,744
#3
'polymerase chain reaction'/exp OR 'enzyme immunoassay'/exp OR 'immunoassay'/exp OR 'virus antibody'/exp OR 'enzyme linked immunosorbent assay'/exp OR 'virus envelope protein'/exp OR 'serology'/exp/mj OR 'virus dna'/exp OR 'diagnostic kit'/exp
879,538
#2
screen*
56,735
#1
'genital herpes'/exp OR 'genital herpes simplex' OR 'herpes simplex virus 2'/exp OR 'hsv-2' OR 'simplexvirus'/exp OR 'genital herpes' OR 'herpes simplex'/de

EMBASE Intervention Search, 3-31-16

Query	Results	No.
#1	'genital herpes simplex'/exp OR 'genital herpes simplex' OR 'herpes simplex virus 2'/exp OR 'herpes simplex virus 2' OR 'hsv-2'/exp OR 'hsv-2' OR 'simplexvirus'/exp OR 'simplexvirus' OR 'genital herpes'/exp OR 'genital herpes' OR 'herpes simplex'/exp OR 'herpes simplex'	**69,804**
#2	screen*	**952,275**
#3	'polymerase chain reaction'/exp OR 'enzyme immunoassay'/exp OR 'immunoassay'/exp OR 'virus antibody'/exp OR 'enzyme linked immunosorbent assay'/exp OR 'virus envelope protein'/exp OR 'serology'/exp/mj OR 'virus dna'/exp OR 'diagnostic kit'/exp	**863,767**
#4	#1 AND (#2 OR #3)	**14,647**
#5	'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR ('control':ab,ti OR 'controlled':ab,ti AND 'trial':ab,ti)	**5,222,268**
#6	#4 AND #5	**3,855**
#7	#1 AND #3	**12,028**
#8	#7 AND 'systematic review'/exp	**25**
#9	#7 AND #5	**3,184**
#10	'case control study'/exp OR 'cohort analysis'/exp OR 'epidemiological study' OR 'cross-sectional study'/exp OR 'organizational case study' OR 'crossover procedure'/exp OR 'seroepidemiologic study' OR 'epidemiology'/exp OR	**2,756,145**

Appendix B1. Detailed Methods

Query	Results	No.
	'multicenter study'/exp OR 'multicenter study (topic)'/exp OR 'evaluation research'/exp	
#11	#7 AND #10	**1,929**
#12	#8 OR #9 OR #11	**4,431**
#13	#12 NOT #6	**1,247**
#14	'herpes simplex'/exp/mj/dm_di OR ('herpes simplex'/exp/mj AND virology) AND 'herpes simplex virus 2'/exp/mj AND immunology OR 'genital herpes'/exp/mj/dm_di OR ('simplexvirus'/exp/mj AND immunology) OR ('genital herpes'/exp/mj AND virology)	**4,062**
#15	#14 AND 'systematic review'/exp	**5**
#16	#14 AND #5	**1,237**
#17	#14 AND #10	**373**
#18	#15 OR #16 OR #17	**1,490**
#19	#12 OR #18	**5,477**
#20	#19 NOT #6	**2,269**
#21	psychosocial AND test* OR (emotional AND test*) OR (emotional AND impact) OR (diagnosis AND psychosocial) OR (screen* AND psychosocial) OR (test* AND impact) OR 'social stigma'/exp OR 'stigma':ab,ti OR 'labeling':ab,ti OR 'anxiety'/exp/mj/dm_et OR 'stereotyping'/exp	**400,515**
#22	#1 AND #21	**823**
#23	#1 AND #21 AND [2015-2016]/py	**62**
#24	'virus shedding'/exp OR 'viral shedding' OR 'disease transmission'/exp	**194,375**
#25	#1 AND #24	**3,819**
#26	#25 AND #5	**871**
#27	acyclovir OR famciclovir OR valacyclovir OR 'antivirus agent'/de OR 'suppressive treatment':ab,ti OR 'suppressive therapy':ab,ti OR suppressive AND agent*:ab,ti OR suppressive AND drug*:ab,ti OR antiviral AND drug*:ab,ti OR therapy:ab,ti OR 'antiviral treatment':ab,ti OR antiviral AND agent*:ab,ti	**197,974**
#28	#1 AND #27	**3,176**
#29	'patient education'/exp OR 'patient education' OR 'counseling'/exp OR 'secondary prevention'/exp OR 'interpersonal communication'/exp OR disclosure OR 'contact examination'/exp OR 'partner notification'	**699,499**
#30	#1 AND #29	**1,081**
#31	'barrier contraception'/exp OR 'barrier protection':ab,ti OR 'condom'/exp OR 'female condom'/exp OR condom*	**24,747**
#32	#1 AND #31	**757**
#33	#28 OR #30 OR #32	**4,843**
#34	#33 AND #5	**1,194**
#35	#6 OR #8 OR #12 OR #20 OR #23 OR #26 OR #34	**7,457**
#36	#6 OR #8 OR #12 OR #20 OR #23 OR #26 OR #34 AND [humans]/lim	**5,187**
#37	#36 AND ([adolescent]/lim OR [adult]/lim)	**2,292**
#38	'pregnant woman'/exp OR 'pregnancy'/exp OR 'pregnancy complication'/de OR 'pregnancy outcome'/exp	**694,355**
#39	#35 AND #38	**323**
#40	#39 NOT #37	**175**
#41	#37 OR #40	**2,467**
#42	#41 AND [medline]/lim	**2,071**
#43	#41 NOT #42	**396**
#44	#37 OR #43	**2,346**
#45	#44 AND [english]/lim	**2,248**
#46	#44 NOT #45	**98**

Query	Results	No.
#47	#45 AND [2015-2016]/py	**185**
#48	#46 AND [2015-2016]/py	**0**

Gray Literature Searches, 5/6/15

ClinicalTrials.gov – searched 5/6/15 with only herpes terms in Advanced Search, no other limits. Search terms: "Herpes Genitalis" or "genital herpes simplex" or "Herpesvirus 2, Human" or "HSV-2" or HSV2 or Simplexvirus or "genital herpes" or "Herpes Simplex" (Yield 20)

WHO ICTRP searched 6/9/15 – Herpes search string as above for ClinicalTrials.gov, searched in the Condition box, and limited to ALL studies (459 records for 357 trials found). Search terms: Herpes Genitalis OR genital herpes simplex OR Herpesvirus 2, Human OR HSV-2 OR HSV2 OR Simplexvirus OR genital herpes OR Herpes Simplex

Grey Literature Searches, 3/31/16

Clinicaltrials.gov – Searched on 3/31/16 with only herpes terms in Advanced Search, and last updated from 2/28/2015 (1 result found)

WHO ICTRP – Searched on 3/31/16 with the herpes terms in the Condition box, and limited to all studies (23 results found). Search terms: Herpes Genitalis OR genital herpes simplex OR Herpesvirus 2, Human OR HSV-2 OR HSV2 OR Simplexvirus OR genital herpes OR Herpes Simplex

Appendix B2. Eligibility Criteria

	Include	Exclude
Populations	**All KQs**: Asymptomatic[a] sexually active adults or adolescents with no clinical history of genital herpes[b], including asymptomatic partners of persons with known genital herpes (i.e., discordant couples) **KQs 1b, 3b, 5b, 6b**: Asymptomatic pregnant women only **KQ 2:** Asymptomatic persons or those previously diagnosed with genital herpes	**All KQs:** Children (age <13 years); persons with HIV infection or other immunosuppressive disorders **KQs 1, 3–7:** Persons previously diagnosed with genital herpes or with current symptoms (e.g., genital ulcers)
Screening	**KQs 1–3:** FDA-approved serologic tests for HSV-2 or "paired testing" for HSV-1 and HSV-2[c]	**KQs 2b, 3:** Serologic tests for HSV-2 that are not commercially available or approved by the FDA; nonserologic tests indicated for the diagnosis of HSV in persons with genital lesions (e.g., cell culture or PCR-based testing); HSV serologic tests that are not type-specific
Interventions	**KQs 4–6:** FDA-approved oral antiviral medications (acyclovir, famciclovir, or valacyclovir) to prevent symptomatic episodes of genital herpes or reduce risk for transmission **KQs 5, 6:** Behavioral counseling interventions, including the following: patient education or counseling; partner notification; barrier protection (e.g., condoms); or combinations of these components **KQ 5b**: Behavioral counseling interventions for seronegative pregnant women that aim to prevent primary genital HSV infection during pregnancy	**KQs 4–6:** Vaccinations; non–FDA-approved pharmacotherapy **KQs 5, 6:** Routine periodic pelvic examinations to screen for gynecologic conditions (e.g., external inspection for genital ulcers)
Comparisons	**KQ 1:** Screened vs. nonscreened groups **KQ 2:** FDA-approved HSV-2 serologic tests vs. HSV Western blot **KQs 3 a, b (psychosocial outcomes)**: Any (or no) comparator **KQ 3b (Cesarean delivery rate)**: Screened vs. nonscreened groups **KQs 4–6a:** Oral antiviral medications vs. placebo **KQ 6b**: Oral antiviral medications vs. placebo or no intervention **KQs 5, 6:** Behavioral counseling interventions vs. attention controls or usual care (e.g., provision of a patient handout on genital herpes) **KQ 7**: Higher vs. lower rates (or frequency) of subclinical viral shedding (e.g., percentage of days of subclinical viral shedding)	**KQs 1, 2, 4–7:** No comparison; nonconcordant historical controls; comparative studies of various interventions (e.g., comparing two antiviral drugs or two different type-specific HSV-2 serologic tests)
Outcomes	**KQs 1a, 5a, 7:** Reduced rates of symptomatic genital herpes; reduced rates of genital herpes transmission measured by partner symptom recognition (or clinician diagnosis) or HSV seroconversion **KQs 1b, 5b:** Reduced rates of neonatal HSV infection; reduced rates of symptomatic genital herpes at delivery **KQ 2:** Sensitivity, specificity, positive predictive value, and negative predictive value	**All KQs:** Cost-effectiveness or cost-related outcomes; transmission of other sexually transmitted infections (e.g., HIV) **KQ 3:** Acceptability of HSV serologic testing

Appendix B2. Eligibility Criteria

	Include	Exclude
	KQ 3: Labeling, anxiety, or false-positive results leading to unnecessary treatment, partner discord, or distress or anxiety around the meaning of HSV-1 results when screening involves a "paired test" (HSV-1 and HSV-2 results reported together), or other psychosocial harms **KQ 3b:** Increased rates of Cesarean delivery (in women with no evidence of active genital lesions at the time of delivery) **KQ 4**: Reduced rates (or frequency) of subclinical HSV-2 viral shedding **KQ 6:** Treatment-related adverse events (e.g., adverse drug reactions related to antiviral medications); psychosocial harms related to counseling or behavioral interventions	
Study designs	**KQs 1, 4–6a:** Randomized, controlled trials **KQs 2, 3:** Good-quality, recent (within 5 years) systematic reviews[d]; trials or observational studies published since the most recent review **KQ 6b**: Randomized, controlled trials and multi-institution antiviral medication pregnancy exposure registries **KQ 7:** Treatment studies included in KQs 4–6 reporting both change in HSV-2 viral shedding and change in a health outcome; prospective cohort studies that follow participants for at least 1 year	All other designs
Setting	Primary care outpatient settings (or similar settings that are applicable to primary care)	All other settings
Language	English	Languages other than English

[a] "Asymptomatic" refers to persons who have never had clinical symptoms of genital herpes (e.g., genital ulcers), not persons with genital herpes who have symptom-free periods between symptomatic recurrences.
[b] Eligible studies with mixed populations (e.g., studies that enroll a subset of participants who are seropositive for HSV without a clinical history of genital herpes) will be included when results are provided separately or can be obtained from the authors.
[c] Studies that test for both HSV-1 and HSV-2 (simultaneously) will be included if they meet other eligibility criteria; however, only the accuracy of test characteristics related to HSV-2 serologic tests will be evaluated.
[d] Previous systematic reviews will be included if they are recent (published within 5 years), of good quality, and are similar in scope to our review. Initial database searches will not be limited by date of publication for these KQs. If no recent, good-quality systematic reviews are identified, all eligible primary studies that address the KQs will be included.

Abbreviations: FDA = U.S Food and Drug Administration; HSV = herpes simples virus; KQ = key question; PCR = polymerase chain reaction.

Randomized Controlled Trials

Criteria

- Initial assembly of comparable groups: Randomized controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: Equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Sources: U.S. Preventive Services Task Force, Procedure Manual, Appendix VII http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual---appendix-vii
Harris et al., 2001.[62]

Studies of Diagnostic Tests

Criteria

- Screening test relevant, available for primary care, adequately described.
- Study uses a credible reference standard, performed regardless of test results.
- Reference standard interpreted independently of screening test.
- Handles indeterminate results in a reasonable manner.
- Spectrum of patients included in study.
- Sample size: Although this is one of the criteria listed in the current procedures manual, we did not consider sample size when assessing study quality, as sample size affects precision of the estimate.
- Administration of reliable screening test.

In addition to the criteria listed in the USPSTF procedures manual, we also considered the criteria described in our Appendix D (which details assessments of individual studies).

Definition of Ratings Based on Above Criteria

Good: Relevant and adequately described study populations for the outcome of interest (i.e., Sensitivity, Specificity), screening test well described in terms of test procedures followed and threshold used for a "positive" or "negative" test, credible reference standard used for outcome of interest (i.e., Sensitivity or Specificity), generally interprets reference standard independently of screening test, outcomes clearly reported and valid, handles indeterminate results in a reasonable manner.

Fair: Mostly includes a relevant and adequately described study population for the outcome of interest (i.e., Sensitivity, Specificity), screening test described although may include some ambiguity about test procedures followed or threshold for a "positive" or "negative" test, credible reference standard mostly used for outcome of interest (i.e., Sensitivity or specificity), interpretation of reference standard may or may not be independent of screening test, outcomes mostly clearly reported although may have some ambiguity regarding how indeterminate results were handled.

Poor: Has fatal flaw such as study population not appropriate for outcome of interest (i.e., Sensitivity, Specificity), screening test improperly administered or not at all described, use of noncredible reference standard, reference and screening test not independently assessed, outcomes not clearly or accurately reported with no information about how indeterminate tests were handled.

Criteria Adapted from: U.S. Preventive Services Task Force, Procedure Manual Appendix VII http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual---appendix-vii
Harris et al., 2001.[62]

Appendix C. Excluded Studies

Exclusion codes:

X1: Not original research
X2: Wrong population
X3: Wrong screening test
X4: Wrong or no intervention
X5: Wrong or no comparator
X6: Wrong outcome
X7: Wrong study design
X8: Non-English
X9: Poor quality

1. Oral acyclovir for genital herpes simplex infection. Med Lett Drugs Ther. 1985 May 10;27(687):41-3. PMID: 3889569. Exclusion Code: X1
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Appendix C. Excluded Studies

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61. Cook RL, Pollock NK, Rao AK, et al. Increased prevalence of herpes simplex virus type 2 among adolescent women with alcohol use disorders. J Adolesc Health. 2002 Mar;30(3):169-74. PMID: 11869923. Exclusion Code: X6
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76. Diagnostics M. HSV-1 & HSV-2 Differentiation Immunoblot IgG 510(k) Summary of Safety and Effectiveness. April 5, 2000 2000. Exclusion Code: X9
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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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247. Wald A. Herpes simplex virus type 2 transmission: risk factors and virus shedding. Herpes. 2004 Aug;11 Suppl 3:130A-7A. PMID: 15319082. Exclusion Code: X1
248. Wald A, Ashley-Morrow R. Serological testing for herpes simplex virus (HSV)-1 and HSV-2 infection. Clin Infect Dis. 2002 Oct 15;35(Suppl 2):S173-82. PMID: 12353203. Exclusion Code: EX7
249. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. Ann Intern Med. 2005 Nov 15;143(10):707-13. PMID: 16287791. Exclusion Code: X7
250. Wald A, Langenberg AGM, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. J Am Med Assoc. 2001;285(24):3100-6. Exclusion Code: X7
251. Wald A, Selke S, Warren T, et al. Comparative efficacy of famciclovir and valacyclovir for suppression of recurrent genital herpes and viral shedding. Sex Transm Dis. 2006 Sep;33(9):529-33. PMID: 16540883. Exclusion Code: X2
252. Wald A, Zeh J, Barnum G, et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann Intern Med. 1996 Jan 1;124(1 Pt 1):8-15. PMID: 7503497. Exclusion Code: X2
253. Wald A, Zeh J, Selke S, et al. Genital shedding of herpes simplex virus among men. J Infect Dis. 2002 Oct 15;186 Suppl 1:S34-9. PMID: 12353185. Exclusion Code: X5
254. Wald A, Zeh J, Selke S, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. N Engl J Med. 2000 Mar 23;342(12):844-50. PMID: 10727588. Exclusion Code: X7
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262. Whitley RJ, Nahmias AJ, Soong SJ, et al. Vidarabine therapy of neonatal herpes simplex virus infection. Pediatrics. 1980 Oct;66(4):495-501. PMID: 7001331. Exclusion Code: X4
263. Whittington WL, Celum CL, Cent A, et al. Use of a glycoprotein G-based type-specific assay to detect antibodies to herpes simplex virus type 2 among persons attending sexually transmitted disease clinics. Sex Transm Dis. 2001 Feb;28(2):99-104. PMID: 11234793. Exclusion Code: X3
264. Wilkinson D, Barton S, Chard S, et al. The psychological consequences in patient undergoing a POCKit HSV-2 test. Int J STD AIDS. 2000 Aug;11(8):551-2. PMID: 10990342. Exclusion Code: X2
265. Williams JR, Jordan JC, Davis EA, et al. Suppressive valacyclovir therapy: impact on the population spread of HSV-2 infection. Sex Transm Dis. 2007 Mar;34(3):123-31. PMID: 17325600. Exclusion Code: X2
266. Witwer M. Serologic testing reveals higher than expected herpes virus infection rates in U.S. population. Fam Plann Perspect. 1989;21(6):279-80. Exclusion Code: X1
267. Wolff MH, Schmitt J, Rahaus M, et al. Clinical and subclinical reactivation of genital herpes virus. Intervirology. 2002;45(1):20-3. Exclusion Code: X2
268. Wutzler P, Doerr HW, Farber I, et al. Seroprevalence of herpes simplex virus type 1 and type 2 in selected German populations-relevance for the incidence of genital herpes. J Med Virol. 2000 Jun;61(2):201-7. PMID: 10797375. Exclusion Code: X5
269. Yin YP, Wu Z, Lin C, et al. Syndromic and laboratory diagnosis of sexually transmitted infection: A comparative study in China. Int J STD AIDS. 2008;19(6):381-4. Exclusion Code: X5
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271. Zimet GD, Rosenthal SL, Fortenberry JD, et al. Factors predicting the acceptance of herpes simplex virus type 2 antibody testing among adolescents and young adults. Sex Transm Dis. 2004 Nov;31(11):665-9. PMID: 15502674. Exclusion Code: X6

Appendix D Table 1. Quality Ratings of Studies Assessing the Accuracy of Serologic Screening Tests for HSV-2 (Key Question 2)

First Author, Year	Was the cutpoint used to determine test positivity adequately described (or referenced)?	Were population selection criteria clearly described?	Did the whole or a random selection of the participants receive the Western blot?	Did all participants receive the Western blot regardless of serologic screening test results?	Were the serologic test results and Western blot results interpreted independently?
Lingappa, 2010[73]	Yes	Yes	Yes	Yes	Yes
Mark, 2007[65]	Yes	Yes	Yes	Yes	NR/CND
Ng'ayo, 2010[74]	Yes	Yes	Yes	Yes	NR/CND
Delany-Moretlwe, 2009[75]	Yes	Yes	Yes (random selection)	Yes	NR/CND
Summerton, 2007[95]	Yes	NR/CND	See comments	No	NR/CND
Ashley-Morrow, 2004[66]	Yes	Yes	NR/CND	Yes	Yes
Mujugira, 2011[67]	Yes	Yes	Yes	Yes	Yes
Smith, 2009[68]	Yes	Yes	Yes	Yes	NR/CND
Golden, 2005[69]	Yes	Yes	Yes	No	NR/CND
Morrow, 2005[70]	Yes	Yes	NR/CND	No	NR/CND
Hogrefe, 2002[71]	Yes	Yes	Yes	Yes	NR/CND
Gamiel, 2008[96]	Yes	No	Yes	Yes	NR/CND
Van Dyck, 2004[72]	Yes	No	Yes	Yes	NR/CND
Ashley, 1998 [97]	No	No	No	Yes	NR/CND

Appendix D Table 1. Quality Ratings of Studies Assessing the Accuracy of Serologic Screening Tests for HSV-2 (Key Question 2)

First Author, Year	What was the overall attrition?	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?	Did the study have high attrition raising concern for bias?	What was the method used to handle missing data?	Quality	Comments
Lingappa, 2010[73]	5%	Yes	Yes	No	Excluded	Good	Five percent (N=26) samples had equivocal WB results and were excluded from the analyses. The characteristics of the subset of participants included in this analysis were not described (only those of the overall community cross-sectional sample, N=1,124). There was no description of whether participants had current or previous symptoms consistent with genital herpes.
Mark, 2007[65]	11%	Yes	Yes	No	Excluded	Good	NA
Ng'ayo, 2010[74]	≥ 6% (see comments)	Yes	Yes	Unclear	Excluded	Fair	Characteristics of population not described (included prior symptoms of genital herpes); all equivocal and indeterminate results (on both WB and serologic screening test) were excluded from sensitivity and specificity calculations. For higher cutoff values on the Focus test, the number of equivocal values was high (approximately 40% of the sample tested).
Delany-Moretlwe, 2009[75]	Unclear	NA	Yes	No	NA	Fair	A random sample of results from the larger sample (N=210) were compared with WB; the results were used to extrapolate sensitivity/specificity in the full sample. Handling of Indeterminate or equivocal test results was not reported. Results for subgroups of participants (by age and HIV status) were given but no measure of variance (confidence interval) was reported for the subgroups.

Appendix D Table 1. Quality Ratings of Studies Assessing the Accuracy of Serologic Screening Tests for HSV-2 (Key Question 2)

First Author, Year	What was the overall attrition?	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?	Did the study have high attrition raising concern for bias?	What was the method used to handle missing data?	Quality	Comments
Summerton, 2007[95]	1%	Yes	Yes	No	Excluded	Poor	Specificity outcome was not eligible due to sampling strategy. All participants who had a positive result on at least one of three serologic screening tests had the WB; participants who had a negative result on the three serologic tests were excluded.
Ashley-Morrow, 2004[66]	See comments	Yes	Yes	No	NA	Fair	Samples from some sites (Barcelona and Hanoi) were not considered due to technical issues. Twenty samples were excluded due to equivocal results (2.9%). Subset of samples were compared to the WB and results were used to estimate the sensitivity/ specificity for the overall sample.
Mujugira, 2011[67]	4%	Yes	Yes	No	Excluded	Good	Unequivocal test results (4%) excluded from sensitivity/ specificity calculations.
Smith, 2009[68]	2%	NA	Yes	No	Excluded	Fair	Blinding of outcome assessors is NR (but the tests were conducted at different sites); does not appear that data were missing but equivocal results were excluded.
Golden, 2005[69]	5%	NR/CND	Yes	No	Excluded	Fair	Unclear if test results were interpreted blindly; excluded atypical WB results
Morrow, 2005[70]	8%	NR/CND	Yes	No	Excluded	Fair	Testing was not performed on the whole sample; only the MSM sample was reported to be randomly selected (the other sample was NR). All participants did not receive WB; assuming blinded
Hogrefe, 2002[71]	2%	NR/CND	Yes	No	See comments	Fair	WB atypical tests were excluded; indeterminate HerpeSelect® serologic test results were considered positive.

Appendix D Table 1. Quality Ratings of Studies Assessing the Accuracy of Serologic Screening Tests for HSV-2 (Key Question 2)

First Author, Year	What was the overall attrition?	Were withdrawals from the study explained (post-enrollment)?	Were methods for calculating accuracy clearly reported and valid?	Did the study have high attrition raising concern for bias?	What was the method used to handle missing data?	Quality	Comments
Gamiel, 2008[96]	NR	NA	NR/CND	NA	NR	Poor	Methods for calculating sensitivity/specificity is not reported, specifically how indeterminate values were handled. Sample size for the Biokit HSV-2 Rapid Test analysis for HIV-negative subgroup is not reported.
Van Dyck, 2004[72]	Unclear	NA	Yes	NR/CND	NR	Fair	Sensitivity was estimated by taking a random sample of serologic test results that were concordant (positives and negatives) and all those that were discordant compared with the monclonal antibody-blocking enzyme immunoassay and comparing those with the WB. The handling of indeterminate tests is unclear; however, it appears that a positive test was defined as equal to or greater than 1.1, and lower results were considered negative.
Ashley, 1998[97]	2%	NA	Yes	No	Excluded	Poor	Characteristics of study sample are not reported. Risk of spectrum bias; samples were chosen based on known, clear profiles to HSV-1 and HSV-2.

Abbreviations: CND = cannot determine; N = number; NA = not applicable; NR = not reported; MSM = men who have sex with men; WB = Western Blot.

Appendix D Table 2. Quality Ratings of Studies Assessing the Harms of Serologic Screening for HSV-2 (Key Question 3)

First Author, Year	Were eligibility criteria clearly described?	Were subjects[a] representative of the overall source population?	Were criteria used to assess prior symptoms clearly described?	What was the overall attrition?	Did the study have high attrition raising concern for bias?	Were outcomes prespecified /defined and adequately described?	Were outcome measures valid and reliable?	Quality	Comments
Smith, 2000[98]	Partially	NR/CND	No	46%	Yes	Yes	Yes	Poor	High risk of selection bias and high attrition (with people having significant anxiety less likely to follow-up). Study population was recruited from persons presenting to sexual health clinics in Australia. How authors determined symptom status was not described.
Edlow, 2012[99]	No	NR/CND	No	NR	NR/CND	Yes	Unclear	Poor	This is an abstract that has limited description of methods, including no description of eligibility criteria. Overall, there is a high risk of selection bias. Personal communication from the author indicated that "all comers" were enrolled. The author states that participants were not explicitly treatment-seeking or symptomatic; however, the percent with no prior or current symptoms is unknown. Validity of the GHQ-12 to assess harms (e.g., whether it is sensitive enough) in this context is uncertain.
Mark, 2008[77]	Partially (see comments)	NR/CND	No	72%	Yes	Yes	Yes	Poor	High risk of selection bias, high attrition, and no control group. Very small sample with just 3 WB confirmed positives completing the follow up. Eligibility criteria are not clear about determination of history of genital sores or genital herpes, and are not clear about whether participants were required to be

Appendix D Table 2. Quality Ratings of Studies Assessing the Harms of Serologic Screening for HSV-2 (Key Question 3)

First Author, Year	Were eligibility criteria clearly described?	Were subjects[a] representative of the overall source population?	Were criteria used to assess prior symptoms clearly described?	What was the overall attrition?	Did the study have high attrition raising concern for bias?	Were outcomes prespecified /defined and adequately described?	Were outcome measures valid and reliable?	Quality	Comments
									asymptomatic. Given the heavy reliance on flyers and ads for recruitment, population is more likely a group with possible reasons to want testing.
Rosenthal, 2006[79]	No	NR/CND	No	19%	Yes	Yes	Yes	Fair for HRQOL outcomes; Poor for all other outcomes	High risk of selection bias, very high attrition, no concurrent control group that was not screened. Participants required to have no known history of genital herpes; criteria used to determine symptoms was not described. We rated herpes-related QOL data as fair quality; the lack of a control group for this outcome is less concerning since the questions are specific to having a genital herpes diagnosis.
Melville, 2003[78]	Yes	No	No	Of people invited 67% participated (24/36)	Yes	Yes	Yes	Fair	High risk of selection bias; participants were selected from various sites using different recruitment procedures. It is not clear how many were eligible at each site. Authors note 67% of those invited agreed to participate. Authors used predefined semistructured interviews to elicit psychosocial outcomes related to serologic testing. The questionnaire is not shown. Only themes reported by three or more participants were reported as results, so less

Appendix D Table 2. Quality Ratings of Studies Assessing the Harms of Serologic Screening for HSV-2 (Key Question 3)

First Author, Year	Were eligibility criteria clearly described?	Were subjects[a] representative of the overall source population?	Were criteria used to assess prior symptoms clearly described?	What was the overall attrition?	Did the study have high attrition raising concern for bias?	Were outcomes prespecified /defined and adequately described?	Were outcome measures valid and reliable?	Quality	Comments
									common outcomes and potentially serious outcomes (e.g., suicidality) may have occurred in as many as two participants without being reported here.
Hallfors, 2015[45]	Yes	No	No	Unclear	NR/CND	No	Unclear	Poor	Participants were orphans selected from 26 primary schools in Nyanza Province, Kenya. It is unclear whether participants were asked about history of signs/ symptoms of genital herpes. Proportion of youth who declined to participate was not reported. Data on the psychosocial response at disclosure appears to have been collected on all 28 participants who tested positive. Outcome measures are not described; research staff and interviewers coded participant and caregiver responses to disclosure. Results were not based on patient-reported (or caregiver reported) measures of psychosocial harms.
Richards, 2007[88]	Yes	NR/CND	No	Of those testing HSV-2 positive (N=87), 89% completed follow-up	Yes	Yes	Mixed	Poor	High risk of selection bias; unclear if subjects who agreed to participate are similar to the overall source population. Recruitment was not based on the presence or absence of prior symptoms; half of participants were HSV-2 positive or had a prior diagnosis of genital herpes. Criteria for determining

Appendix D Table 2. Quality Ratings of Studies Assessing the Harms of Serologic Screening for HSV-2 (Key Question 3)

First Author, Year	Were eligibility criteria clearly described?	Were subjects[a] representative of the overall source population?	Were criteria used to assess prior symptoms clearly described?	What was the overall attrition?	Did the study have high attrition raising concern for bias?	Were outcomes prespecified /defined and adequately described?	Were outcome measures valid and reliable?	Quality	Comments
									prior diagnosis of genital herpes are not described. Of those contacted via letter (N=5,703), 17% responded and agreed to be contacted. Of those who agreed to be contacted (N=955), 36% agreed to enroll and have HSV-2 testing, 29% declined to participate, 33% could not be contacted, and 2% were ineligible. Of those who tested HSV-2 positive (N=87), 89% completed follow up. Many outcomes were general quality of life or mood state; it is unclear if these are valid measures of the harms associated with HSV-2 screening.

[a] Are they generally asymptomatic persons with no prior history of genital herpes recruited from primary care settings? Is the sample that participated similar to the overall source population?

Abbreviations: CND = cannot determine; N = number; NA = not applicable; NR = not reported; QOL = quality of life; WB = Western Blot.

Appendix D Table 3. Quality Ratings of Studies of Antiviral Medications on HSV-2 Viral Shedding, Symptomatic Episodes, and Transmission (Key Questions 4 and 5)

First Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Are baseline characteristics similar between groups?	What was the overall attrition	What was the differential attrition?
Corey, 2004[76] Kim, 2008[83]	Yes	Yes	Yes	22%	2%
Mujugira[84]	Yes	NR/CND	Yes	66%	2%
Sperling, 2008[81]	Yes	NR/CND	Yes	29%	1.3%
Leone, 2007[82]	Yes	Yes	Yes	23%	NR

First Author, Year	Did the study have high differential attrition (>10%) or overall high attrition generally 20%) raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Were outcome measures valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of follow up adequate to assess the outcome?
Corey, 2004[76] Kim, 2008[83]	No	No	Yes	Yes	NR/CND	Yes	Yes
Mujugira[84]	Yes	NR/CND	Yes	Yes	Yes	NR/CND	Yes
Sperling, 2008[81]	Yes	No	Yes	Yes	Yes	NR/CND	Yes
Leone, 2007[82]	Yes	NR/CND	Yes	Yes	Yes	NR/CND	Yes

Appendix D Table 3. Quality Ratings of Studies of Antiviral Medications on HSV-2 Viral Shedding, Symptomatic Episodes, and Transmission (Key Questions 4 and 5)

First Author, Year	What was the method used to handle missing data?	Did the study use acceptable statistical methods? ITT vs. per protocol; adjustment for factors?	Was compliance to study medication adequate?	Quality	Comments
Corey, 2004[76] Kim, 2008[83]	Data for subjects who did not reach an end point were censored as event-free periods ending on the last day that the absence of the end point was confirmed.	Yes	Yes	Fair	More couples randomized to placebo withdrew; per authors withdrawal occurred because more source partners had frequent symptoms. Missing data were censored (as event-free periods). However, differential attrition was relatively low (2%).
Mujugira[84]	Modeling was used to impute some data.	Yes	Yes	Fair	Overall attrition is high; analysis accounted for some of the missing data.
Sperling, 2008[81]	Missing data were excluded.	Yes	NR/CND	Fair	This is a crossover RCT. There was an overall high rate of attrition (29 %); differential attrition was low.
Leone, 2007[82]	Unclear; modeling was used to estimate differences between groups and likely some data was imputed. However, participants who provided no swabs were excluded from analysis.	Yes	Yes	Fair for KQ 4 and 5 outcomes	This is a cross-over RCT; overall attrition is high (23%). Handling of missing data is unclear for some outcomes.

Abbreviations: CND = cannot determine; NR = not reported; RCT = randomized controlled trial.

Appendix D Table 4. Quality Ratings of Studies Assessing Harms of Preventive Interventions (Key Question 6)

First Author, Year	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of follow up adequate for harms assessment?	Quality	Comments
Sperling, 2008[81]	No	No	NR/CND	Yes	Fair	Adverse events were assessed at every visit after discussion with the subject and review of the subject's diary. Harms do not appear to have been prespecified.
Leone, 2007[82]	No	No	NR/CND	Yes	Poor	Harms are reported but not prespecified for well-defined; harms are only reported for the overall sample and not the subgroup of participants with no prior history of genital herpes.

Abbreviations: CND = cannot determine; NR = not reported.

Appendix E Table 1. Results of Included Studies Assessing the Accuracy of HerpeSelect for HSV-2 (Key Question 2)

Author, Year Country	N Eligible (N analyzed)	Equiv. Tests Excluded[a] (Cut-point[b])=N	Cutpoint: Sensitivity (95% CI)	Cutpoint: Specificity (95% Ci)	Cutpoint: PPV (95% CI)	Cutpoint: NPV (95% CI)
Ashley-Morrow, 2004[66] Multinational	NR (675)	WB=9[c] HS=11	1.1: 97.0 (NR) 3.5: 90.0 (NR)	1.1: 89.0 (NR) 3.5: 96.0 (NR)	1.1: 86.0 (NR) 3.5: 86.0 (NR)	1.1:98.0 (NR) 3.5:98.0 (NR)
Delany-Moretlwe, 2009[75] South Africa	210 (98)[d]	NR	1.1: 98.0 (95.0 to 100.0) 3.5: 94.0 (89.0 to 100.0)	1.1: 61.0 (48.0 to 74.0) 3.5: 87.0 (67.0 to 100)	NR	NR
Golden, 2005[69] U.S.	Unclear[e] (1.1=61) (1.5=55) (2.0=50) (2.5=47) (3.0=43)	WB (all) = 5 HS (1.1) =NR HS (1.5) = 9 HS (2.0) =18 HS (2.5) =26 HS (3.0)= 30	NR	NR	1.1: 84.0 (NR) 1.5: 85.0 (NR) 2.0: 92.0 (NR) 2.5: 96.0 (NR) 3.0: 98.0 (NR)	NR
Hogrefe, 2002[70] African Countries	785 (765)	HS =5	1.1: 99.6 (NR) 1.5: 98.0 (NR) 2.1: 95.9 (NR) 2.5: 93.7 (NR) 3.1: 90.5 (NR)	1.1: 88.0 (NR) 1.5: 93.0 (NR) 2.1: 94.9 (NR) 2.5: 96.5 (NR) 3.1: 97.8 (NR)	NR	NR
Lingappa, 2010[73] Uganda	493 (467)	WB= 25	1.1: 99.5 (98.5 to 100.1) 2.2: 96.4 (94.4 to 98.3)	1.1: 70.2 (64.1 to 76.1) 2.2: 92.4 (87.0 to 96.9)	NR	NR
Mark, 2007[65] U.S.	100 (89)	HS=3	1.1: 100.0 (30.9 to 100)	1.1: 94.1 (86.3 to 97.8)	1.1: 37.5 (10.2 to 74.1)	1.1: 100 (94.3 to 100)
Morrow, 2005[70] U.S.	1749 (782)	WB= 37 HS= 26	1.1: 99.2 (96.3 to 100.0)	1.1: 93.2 (91.8 to 94.6)	1.1: 80.5 (76.9 to 84.2)	1.1: 99.7 (98.9 to 100)
Mujugira, 2011[67] African Countries	3408 (3290)	WB=109	1.1: 98.3 (NR) 2.1: 93.9 (NR) 3.5: 82.9 (NR)	1.1: 80.3 (NR) 2.1: 90.5 (NR) 3.5: 95.1 (NR)	NR	NR
Ng'ayo, 2010[74] Kenya Gen 1[6]	250 (1.1:229) (3.5:154)	WB: 15 HS (1.1) = 6 HS (3.5)=90	1.1: 98.6 (95.1 to 99.8) 3.5: 97.2 (92.8 to 99.3)	1.1: 63.5 (52.9 to 73.0) 3.5:93.0 (83.3 to 97.1)	1.1: 82.1 (NR) 3.5: 96.0 (NR)	1.1=96.4 (NR) 3.5: 96.4 (NR)

Appendix E Table 1. Results of Included Studies Assessing the Accuracy of HerpeSelect for HSV-2 (Key Question 2)

Author, Year Country	N Eligible (N analyzed)	Equiv. Tests Excluded[a] (Cut-point[b])=N	Cutpoint: Sensitivity (95% CI)	Cutpoint: Specificity (95% Ci)	Cutpoint: PPV (95% CI)	Cutpoint: NPV (95% CI)
Ng'ayo, 2010[74] Kenya Gen 2[f]	250 (1.1:233) (3.5:179)	WB=15 HS (1.1) =6 HS (3.5)=64	1.1: 99.3 (96.2 to 99.8) 3.5: 99.2 (95.6 to 99.8)	1.1: 52.3 (97.6 to 58.0) 3.5:94.9 (73.3 to 92.2)	1.1: 77.4 (NR) 3.5: 94.0 (NR)	1.1=97.8 (NR) 3.5: 97.8 (NR)
Smith, 2009[68] Kenya	120 (99)	HS=1	1.1:100 (86.0 to 100.0) 3.5:80.0 (59.0 to 93.0)	1.1: 41.0 (30.0 to 53.0) 3.5: 80.0 (70.0 to 89.0)	NR	NR
Van Dyck, 2004[72] African Countries	330 (NR)	NR	1.1: 100 (NR)	1.1: 97.5 (NR)	NR	NR

[a] This refers to the number of samples that were excluded from the sensitivity, specificity, PPV or NPV calculation because of an equivocal, indeterminate, or uninterpretable result. Other samples that were eligible may have been excluded for other reasons (e.g., insufficient serum sample).
[b] Cutpoint refers to the cutoff value at or above which the test is considered positive.
[c] Two of these were equivocal by Western blot and HerpeSelect.®
[d] Sensitivity and specificity for whole sample (210) were calculated using the results of 98 participants who had results compared with Western blot. Handling of equivocal tests is unclear.
[e] These numbers and estimates refer to the subgroup of participants who had no clinical evidence of genital herpes.[69]
[f] This study reported estimates separate for the first generation and second generation HerpeSelect.®

Abbreviations: CI = confidence interval; equiv. = equivocal; HS = Focus HerpeSelect®; HSV-2 = Herpes Virus Simplex type 2; N = number; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; WB = Western blot.

Appendix E Table 2. Characteristics and Results of Included Studies Assessing the Accuracy of Biokit Rapid HSV-2 (Key Question 2)

Author, year Country	N eligible (N analyzed); Equiv. tests excluded (N)	Population; Country	Age, Mean (SD)	%F	%non-White	% co-morbid STI	% HSV-1	Results: Sens: (95%CI) Spec: (95% CI)	Results: PPV (95% CI) NPV (95% CI)
Lingappa, 2010[73] Good	493 (467) N excluded: 25 (WB)	Adults participating in a study of genital herpes sero-prevalence and incidence, Uganda	NR	NR	NR	12 (HIV=1)	NR	Sens; 86.4 (83.1 to 89.7) Spec: 97.0 (94.3 to 99.0)	NR
Morrow, 2005[70] Fair	1749 (782) N excluded: 63[a]	Two populations enrolled: (1) Adult MSM screened for enrollment in a clinical trial assessing acyclovir to reduce HIV transmission and (2) Consecutive serologic samples submitted for HSV WB testing at the University of WA Virology lab, United States	NR	O	NR	NR	64 (WB)	Sens: 90.5 (86.1 to 94.0) Spec: 98.4 (97.5 to 99.3)	PPV: 94.5 (90.5 to 97.3) NPV: 99.7 (98.9 to 100)
Ng'ayo, 2010[74] Fair	250 (233) N Excluded: 15 (WB); 3 (Biokit)	Adult men who worked in the fishing industry who reported being sexually active in the previous 2 weeks, Kenya	NR (all ≥ 18 y)		NR	NR	NR	Sens: 66.0 (57.9 to 73.2) Spec: 90.9 (83.2 to 95.4)	PPV: 92.2 (NR) NPV: 62.3 (NR)
Van Dyck, 2004[72] Fair	330 (NR)	Adults who were enrolled in a study on factors determining the spread of HIV, Kenya, Zambia, Benin, Cameroon	NR (all 15-49 y)	NR	NR	NR	NR	Sens: 83.0 (NR) Spec: 95.0 (NR)	NR

[a] This study also assessed the accuracy of HerpeSelect. Samples that were equivocal on HerpeSelect (n=26) or Western blot (n=37) were not tested with Biokit Rapid HSV-2.

Abbreviations: CI = confidence interval; F = female; HIV = human immunodeficiency virus; HSV = herpes simplex virus; N = number; SD = standard deviation; sens = sensitivity; spec = specificity; PPV = positive predictive value; STI = sexually transmitted infection; NPV = negative predictive value; NR = not reported; WA = Washington; y = year

Appendix E Table 3. Characteristics and Results of Included Studies Assessing Harms of Serologic Screening for Genital Herpes (Key Question 3)

Author, Year Study Design Quality	Population; Country	Age, Mean (SD)	%F	% non- White	% co-morbid STI	Results
Melville, 2003[78] Qualitative Fair	Patients at 4 clinics (STD, maternal and infant care, family medicine, virology research) with positive HSV-2 serology; Age 14 or older, able to communicate in English, with HSV-2 infection determined by WB but no history of genital herpes United States (24)	35 (range 19 to 55)	58	25	NR	Short-term emotional responses: N (%)[a] • Denial: 9 (38) • Confusion: 8 (33) • Distress: 6 (25) • Sadness: 4 (17) • Disappointment: 4 (17) • Self-blame: 3 (13) • Surprise: 12 (50.0%) • Relief to know: 5 (20.8%) • "Why me?": 3 (12.5%) Short-term psychosocial responses: N (%)[a] • Fear of telling current partner: 11 (46) • Fear of telling past partner(s): 4 (17) • Anger at source partner: 6 (25) • Guilt about acquiring or transmitting: 5 (21) • Concern about transmitting to child: 4 (17) • Decreased libido: 3 (12.5%) Perceived ongoing responses: N (%)[a] • Feeling socially stigmatised: 8 (33) • Feeling like "damaged goods": 8 (33) • Fear of telling future partner(s): 12 (50) • Feeling sexually undesirable: 10 (42) • Relationship problems after diagnosis: 8 (33) • Increased commitment to current partner: 3 (13) • Relived to discover both have HSV-2: 3 (13) • Reluctance toward future relationships: 3 (13) • Acceptance: 14 (59) • Concern about transmitting to partner: 11 (46) • Sex avoidance due to social responsibility: 8 (33) • Concern of transmitting to newborn: 7 (29)

Appendix E Table 3. Characteristics and Results of Included Studies Assessing Harms of Serologic Screening for Genital Herpes (Key Question 3)

Author, Year Study Design Quality	Population; Country	Age, Mean (SD)	%F	% non- White	% co-morbid STI	Results
Rosenthal, 2006[79] Cohort Study Fair	Individuals (aged 14–30 years) without a history of genital herpes recruited from various settings (an urban university; STD clinics; primary care, and adolescent clinics. Participants completed a questionnaire and were offered free HSV-2 antibody testing. (HSV-2 positive= 33)	24 (3.6)	88	52	NR; 46% of sample recruited from STI clinic	Genital herpes HRQOL[b] at 3 months: Most endorsed items (% endorsed as "'very'' or ''quite''): "It is difficult to forget that I have herpes" (63) "I worry about giving herpes to someone"(56) "I worry about people I know finding out I have herpes" (48) "I feel insecure about personal (intimate) relationships because of herpes" (30) "I get depressed about having herpes" (30) "I feel angry about having herpes" (30) "I worry that people will reject me if they know I have herpes" (30)

[a] These items were expressed by at least three individuals during Focus groups. Items described as short-term relate to initial reactions. Those categorized as "perceived ongoing" were experienced by participants months after diagnosis.
[b] Genital herpes HRQOL is a 20-item measure which addresses issues such as feelings of shame associated with having genital herpes.[80] In this study, participants responded to each item using a 4-point response ranging from "very" to "not at all." "Very" and "quite" were considered to be indicative of endorsing the experience described in individual items.

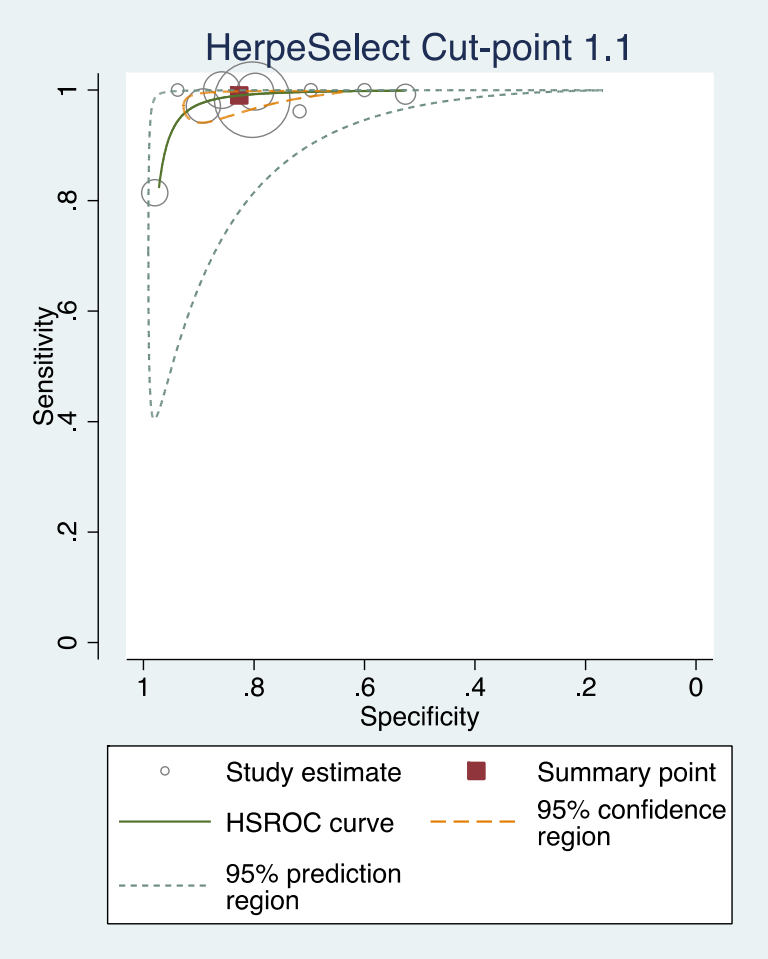
Abbreviations: NR = not reported; HRQOL = health related quality of life; HSV = Herpes simplex virus; SD = standard deviation; STI = sexually transmitted infection; SD = standard deviation; HRQOL = health related quality of life.

Appendix E Table 4. Characteristics and Results of Included Studies Assessing Harms of Preventive Interventions (Key Question 6)

Author, year Study Design Quality	G1 (N) G1 (N)	Duration (wks)	Population	Recruitment Setting; Country	HSV-2 test	Mean age (SD)	% F	% Non-white	% HSV-1 positive	Results
Sperling, 2008[81] RCT (crossover) Fair	Total (63) Valacyclovir 1g daily first (36) Placebo first (37)	8 active; 8 placebo	Adults seropositive for HSV-2 with no active lesions or symptoms consistent with genital herpes and no history of recurrent or undiagnosed symptoms consistent with genital herpes	13 clinical settings (STI clinics, primary care clinics, and gynecology practices) United States	HerpeSelect®	37 (NR)	75	35	56-57	% of participants reporting adverse events: Dizziness G1: 6 G2: 2 Headache G1: 5 G2: 6 Nausea G1: 5 G2: 2 p-value NR*

Abbreviations: F= female; G = Group; HSV = herpes simplex virus; IQR = Interquartile range; mg = milligrams; N = number; NR = not reported; wks = weeks; RCT = randomized controlled trials; SD = standard deviation; STI= sexually transmitted infection.

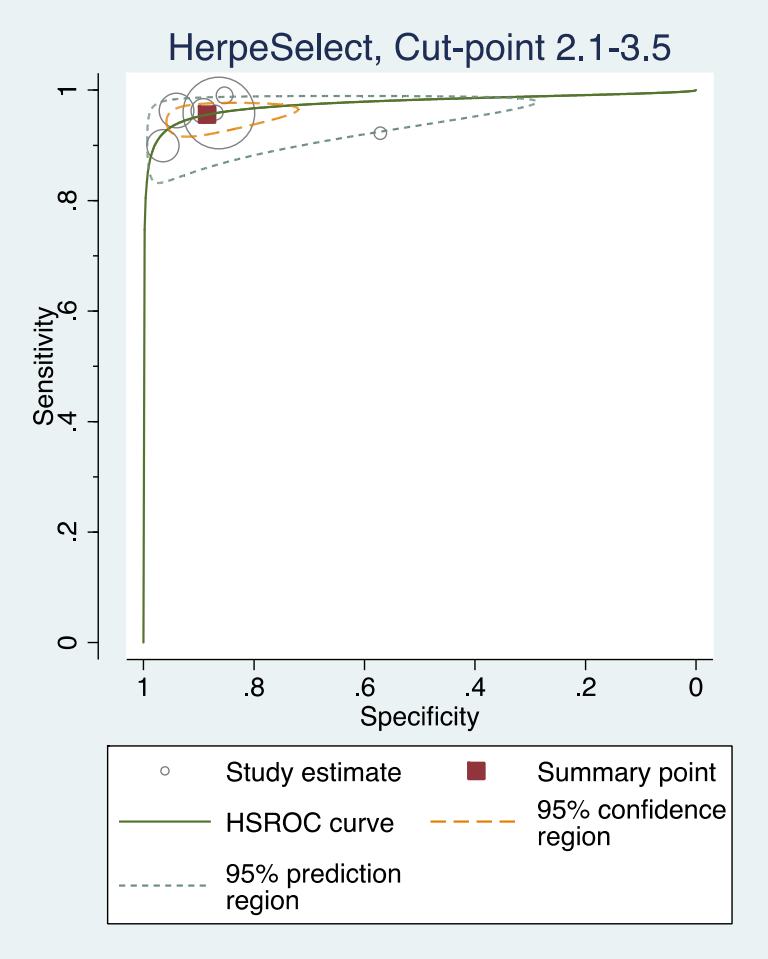
Appendix E Figure 1. Hierarchical Summary Receiver Operating Curve for HerpeSelect, Cut-Point of 1.1[a]



[a] This HSROC compares sensitivity and specificity for the 10 studies reporting on the accuracy of HerpeSelect® at the manufacturer's cutpoint for a positive test (1.1).

Abbreviations: HROC= hierarchical summary receiver-operating curve

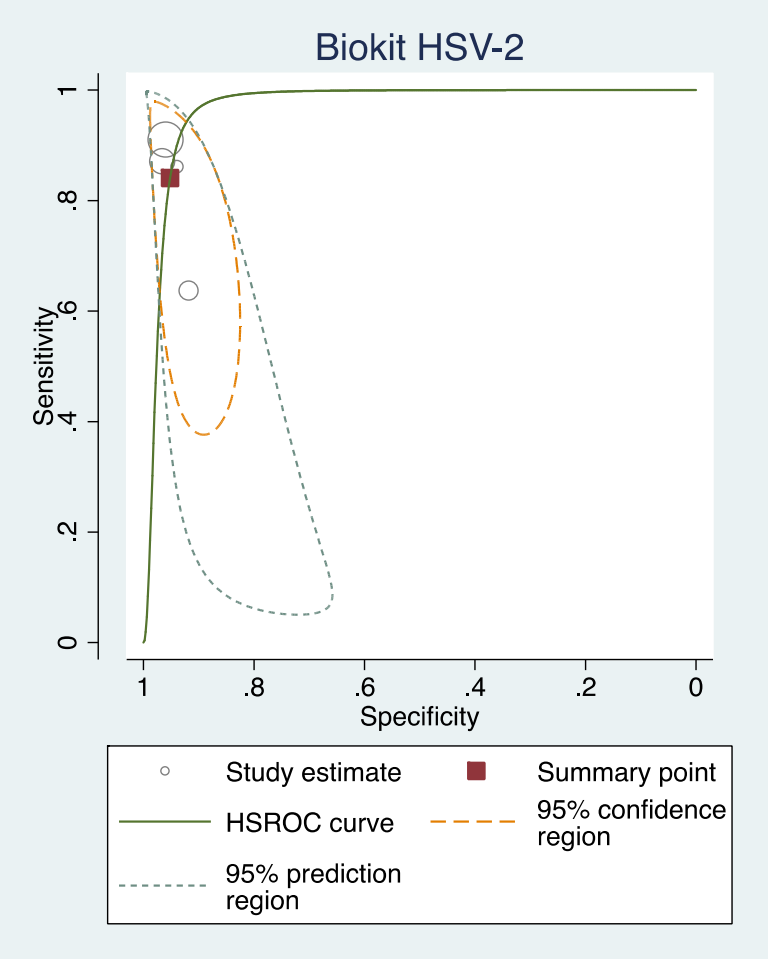
Appendix E Figure 2. Hierarchical Summary Receiver Operating Curve for HerpeSelect, Higher Cut-Points (2.1 to 3.5)[a]



[a] This HSROC compares sensitivity and specificity for the 7 studies reporting on the accuracy of HerpeSelect® at cut-points between 2.1 and 3.5.

Abbreviations: HROC= hierarchical summary receiver-operating curve

Appendix E Figure 3. Hierarchical Summary Receiver Operating Curve for Biokit HSV-2[a]



[a] This HSROC compares sensitivity and specificity for the 4 studies reporting on the accuracy of BiokitHSV-2.

Abbreviations: HROC= hierarchical summary receiver-operating curve