Screening for Genital Herpes Simplex: Brief Update for the U.S. Preventive Services Task Force

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Herpes simplex virus (HSV) is a DNA virus with 2 subtypes: herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2). Although each is a distinct virus, they share some antigenic components. HSV causes vesicular and ulcerative lesions in healthy individuals and may cause severe systemic disease in neonates and immunosuppressed hosts.[1] Infection with HSV-1 commonly causes oropharyngeal infection, and transmission is primarily by non-genital personal contact, whereas infection with HSV-2 most often results in genital lesions, and transmission is usually sexual.[1,2] However, either virus may cause oropharyngeal or genital infection and can produce mucosal lesions that are clinically indistinguishable.[1,3]

HSV is the most prevalent sexually transmitted disease (STD) in the United States.[3] The most accurate estimates derived from seroprevalence surveys show that 1 person in 5, aged 12 years and older in the United States, has been infected with HSV-2, and the rate is even higher among adults and women.[1] These estimates do not include the contribution of sexually acquired HSV-1 to the epidemic of genital herpes. An estimated 1.6 million new HSV-2 infections occur in the United States annually.[4]

Types of Genital HSV Infections

Primary Infection

In a primary infection, the patient has an initial exposure to HSV and no type-specific antibodies to either HSV-1 or HSV-2 exist at the time of the infection. Lesions may appear 2 to 14 days after exposure and, without antiviral therapy, may persist for an average of 20 days. Lesions begin as tender vesicles that may rupture and ulcerate. Additional symptoms associated with primary infections may include intense pain, dysuria, itching, lymphadenopathy, fever, headache, nausea, malaise, and myalgia. Women may have vaginal discharge. Approximately 75% of patients with primary genital HSV infection are asymptomatic. Viral shedding lasts an average of 12 days and ceases before complete resolution of lesions, if present. Antibody response occurs 2 to 12 weeks after the infection and is lifelong. Unlike protective antibodies to other viruses, antibodies to HSV do not prevent local recurrences.

Non-Primary First-Episode Infections

A non-primary first-episode infection is the first genital HSV infection in an individual who has

Systematic Evidence Reviews serve as the basis for U.S. Preventive Services Task Force (USPSTF) recommendations on clinical prevention topics. The USPSTF tailors the scope of these reviews to each topic. The USPSTF determined that a brief update was needed to assist in updating its 1996 recommendations on screening for genital herpes.

To assist the USPSTF, the Oregon Evidence-based Practice Center, under contract to the Agency for Healthcare Research and Quality (AHRQ), performed a targeted review of the literature published on this topic from 1994 to 2002. This brief update and the updated recommendation statement are available on the AHRQ Web site (www.ahrq.gov/clinic/uspstfix.htm). The recommendation is also posted on the Web site of the National Guideline Clearinghouse™ (www.guideline.gov).

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heterologous HSV antibodies. For example, if an individual acquires a non-primary first-episode HSV-2 infection, he/she would have antibodies against HSV-1 at the time of the genital infection. Because of the partial protection of the preexisting antibodies, symptoms may be fewer and of shorter duration; however, this varies. The duration of lesions in a non-primary first episode averages 15 days, and shedding lasts for approximately 7 days. The clinical presentation of a primary infection cannot be reliably distinguished from a non-primary first-episode infection. The diagnosis is based on type-specific culture and type-specific serology.

Recurrent Infections

Recurrent infections may be symptomatic or asymptomatic. Although genital HSV is a chronic infection, the frequency of symptomatic reactivation decreases over time in a majority of individuals.[5] Most symptoms are localized and can include lesions, pain, itching, and, in women, vaginal discharge. Lesions from recurrent infections are present for approximately 7 days with viral shedding for 4 days.

Asymptomatic Viral Shedding

Asymptomatic viral shedding occurs with intermittent viral reactivation without associated clinical symptoms. A prospective study of HSV-2 seropositive adults randomly tested in family practice clinics indicated high rates of asymptomatic viral shedding.[6] Genital secretions were sampled daily and cultured for HSV-2 over a 3-month period. Sixty-one percent of patients with a previous history of genital herpes and 68% of patients without known genital herpes had asymptomatic shedding. HSV-2 is often transmitted during episodes of asymptomatic shedding. Results of this study indicate that HSV-2 seropositive adults are capable of transmitting genital HSV-2 whether or not they had prior symptoms.

Perinatal Transmission of HSV

HSV can be vertically transmitted to the infant during the antenatal, intranatal, or postnatal periods. A woman experiencing a primary episode of HSV in the third trimester who has not completed seroconversion by the onset of labor has a 33% chance of transmitting the virus to her infant.[7] In contrast, a woman experiencing a recurrent infection of HSV during the intrapartum period has an approximately 3% chance of transmitting to her infant.[7] Of known HSV infected infants, only 30% had either mothers or sexual partners of mothers with symptomatic HSV infection.[1]

Neonatal HSV Infection

Neonatal HSV disease is diagnosed in approximately 1 of every 3,000 deliveries in the United States, resulting in an estimated 1,500 cases annually.[8] Most infections are caused by HSV-2 and 15% to 30% are caused by HSV-1.[9] Infants infected with HSV may be born prematurely and have low birth weights. Congenital HSV infection (approximately 4% of all neonatal infections) can cause microcephaly, hydrocephalus, chorioretinitis, and vesicular skin lesions.[9] Three types of neonatal HSV infection acquired at delivery have been identified: 1) disease localized to the skin, eye, and mouth (SEM); SEM disease is the least severe and does not increase mortality[8]; 2) encephalitis, with or without SEM involvement; and 3) disseminated disease involving multiple sites including the central nervous system (CNS), lung, liver, adrenal, and/or SEM. The clinical presentation is nonspecific and includes lethargy, fever, irritability, and failure to feed at 1 week of age. Mortality is high despite treatment with antiviral therapy. Infants with encephalitis have a 15% increase in mortality, and those with disseminated disease have a 57% increase in mortality compared with infants with SEM disease only. Long-term morbidity is common among infants with both encephalitis and disseminated disease, and may include seizures, psychomotor retardation, spasticity, blindness, or learning disabilities.[9]

HSV Detection Methods

HSV Culture

Viral culture is the gold standard for diagnosis of HSV infection, and has a sensitivity of 50% and a specificity of nearly 100%. A culture may

take 3 to 7 days to process. The sensitivity of HSV culture is related to the HSV type and sample site.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) is a molecular test for HSV DNA. PCR is considered the gold standard for detection of HSV in CNS infections. PCR is available at many large laboratories and takes approximately 1 day to process. Sensitivity is 80% to 90% for specimens obtained from lesions, although sensitivity and specificity vary by laboratory.

Serological Tests

Serological tests are used to detect previous infection with HSV-1 and HSV-2 in asymptomatic patients, or to diagnose infection in a symptomatic patient when culture is not feasible or the clinical syndrome is unclear. Currently available tests are described in Table 1. The Western blot assay is the most validated method for identifying type-specific antibodies and is considered the gold standard.[10,11] The Western blot assay has been used to define the spectrum of clinical manifestations of genital herpes and to study the natural history of unrecognized HSV.[12] The Western blot assay is conducted exclusively at the University of Washington where clinical specimens can be sent and processed. Two type-specific glycoprotein G serological tests are commercially available in the United States. Sensitivity and specificity of these tests are comparable to the Western blot assay.[12] These tests cost $10 to $40 (U.S. dollars).

Antiviral Therapy

Antiviral medications (acyclovir, famciclovir, and valacyclovir) are approved for treatment of genital HSV. These drugs are selective for cells infected with HSV and stop viral replication. They are considered safe and effective when used by otherwise healthy adults. There is limited evidence of acyclovir use and safety during pregnancy. These drugs relieve discomfort caused by HSV lesions, speed healing in uncomplicated primary and recurrent genital HSV infections, and reduce viral shedding. They are used as a short course during recurrent episodes or for chronic daily suppressive therapy.

HSV Education and Prevention

The goals of educating infected individuals and their sexual partners are to assist them in coping with recurrent symptoms and to prevent sexual and perinatal transmission. Specific educational messages recommended by the Centers for Disease Control and Prevention (CDC) include: the natural history of the infection, potential for recurrences, asymptomatic viral shedding and transmission, informing sexual partners of infection, avoiding sexual activity with uninfected partners when symptomatic, antiviral treatment, consistent use of latex condoms to prevent transmission, and risk for neonatal infection during late pregnancy.[13]

A prospective study of asymptomatic HSV-2 seropositive adults randomly tested in family practice clinics described the impact of patient education.[6] Of the participants who reported no previous history of genital herpes despite seropositive test results, 63% reported having typical lesions following education on signs and symptoms of genital HSV infection.[6]

A prospective study of pregnant women evaluated whether education and counseling about symptoms of HSV genital infection would lead to improved recognition.[14] Recognition of active infection could alert clinicians to potential transmission risk during delivery. Women underwent a detailed interview and an HSV serological test using Western blot assay. Women who were HSV-2 seropositive but had no reported or recognized recurrences were followed. After education and counseling regarding genital HSV, 45% of women who were HSV-2 positive but did not report recurrences were able to precisely report symptomatic reactivations of genital HSV.

Previous USPSTF Recommendations

The U.S. Preventive Services Task Force (USPSTF) recommendations for screening for genital herpes were published in 1996 and included[15]:

- Routine screening for genital HSV infection in asymptomatic persons using culture,

Table 1. Comparison of Commercial HSV Type-Specific Antibody Tests with Each Other and the Gold Standard, Western Blot Assay

Test	HerpeSelect® ELISA kit	HerpeSelect® Immunoblot kit	Herpes Western Blot Assay
Manufacturer	Focus Technologies	Focus Technologies	University of Washington
FDA approved	Yes (2000)	Yes (2000)	NA (considered research "gold standard")
Antibodies detected	HSV-1 or HSV-2	HSV-1 and HSV-2	HSV-1 and/or HSV-2
Sensitivity	96%–100%	87%–100%	> 99%
Specificity	97%–100%	98%	> 99%
Collection method	Blood draw (sent to lab)	Blood draw (sent to lab)	Blood draw (sent to University of Washington)
Test location	Various labs	Various labs	University of Washington Virology Department
Result time	1–2 weeks	1–2 weeks	2 weeks
Can be used during pregnancy	Yes	Yes	Yes
Cost of test	$40–$80	$80–$160	$130

Note: Adapted from Ashley RL. Sorting out the new HSV type-specific tests. *Sex Transm Infect*. 2001;77:232–237, and the Herpes Resource Center of the American Social Health Association, June 2003.

ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; HSV, herpes simplex virus; NA, not available.

serology, or other tests, is not recommended (D recommendation).

- Routine screening for genital HSV in asymptomatic pregnant women by surveillance, cultures, or serology, is also not recommended (D recommendation).
- Clinicians should consider asking all pregnant women at the first prenatal visit whether they or their sex partner(s) have had genital herpetic lesions. There is insufficient evidence to recommend for or against routine counseling of women who have no history of genital herpes, but whose partners do have a positive history, to use condoms or abstain from intercourse during pregnancy (C recommendation); such counseling may be recommended on other grounds.
- There is also insufficient evidence to recommend for or against the examination of all pregnant women for signs of active genital HSV lesions during labor and the performance of cesarean delivery on those with lesions (C recommendation).
- There is not yet sufficient evidence to recommend for or against routine use of systemic acyclovir in pregnant women with recurrent herpes to prevent reactivations near term (C recommendation).

Updates

A topic update was conducted by investigators at the University of North Carolina/Research Triangle Institute (UNC/RTI) during 2002 using 2 approaches ("review" and "traditional") and included MEDLINE® searches from 1994–2002. In addition, expert reviewers were contacted for comment. This report and its methods were provided to the USPSTF in an earlier briefing book. A brief update was deemed necessary by the

UNC/RTI update process and expert reviewers because of new literature in areas of testing (HSV-2 specific assays, PCR), effectiveness of condoms and antivirals in reducing transmission, and use of prophylactic medications.

The current update includes new publications since the last USPSTF recommendations. The rationale for screening would be to identify asymptomatic infected individuals capable of unknowingly transmitting HSV to partners and neonates. Identification could occur by serological testing or by education followed by diagnostic testing of newly recognized lesions.

The target population for this update includes adolescents, adults, and pregnant women/neonates. The analytic framework and key questions guiding the literature searches are described in the Figure.

Methods

MEDLINE was searched from 1996–March 2004 (Appendix 1). References cited in the 2002 report and references suggested by expert reviewers were also included. Captured titles and/or abstracts were downloaded and imported into the EndNote® program to create a library. Titles and/or abstracts were dual reviewed for inclusion or exclusion. Full text papers were retrieved and reviewed using specific inclusion/exclusion criteria. Trials of antiviral therapy were rated for quality by 2 independent reviewers using USPSTF criteria (Appendix 2).

Results

One hundred and twenty-seven abstracts and titles were identified from our MEDLINE search. We identified an additional 33 titles from the UNC/RTI report and 27 titles from suggestions of experts and reference lists. We found 13 duplicate titles in our EndNote library. Therefore, we reviewed a total of 174 abstracts and titles (Appendix 3). Seventy-nine full text articles were obtained and reviewed for the update. Further, a systematic review of antenatal HSV screening in the United Kingdom was reviewed.

Key Questions

1a. Does screening for HSV in asymptomatic adolescents and adults reduce symptomatic recurrences and transmission of disease?

No studies were identified that directly evaluated whether screening asymptomatic individuals for genital HSV reduces symptomatic recurrences and transmission of disease.

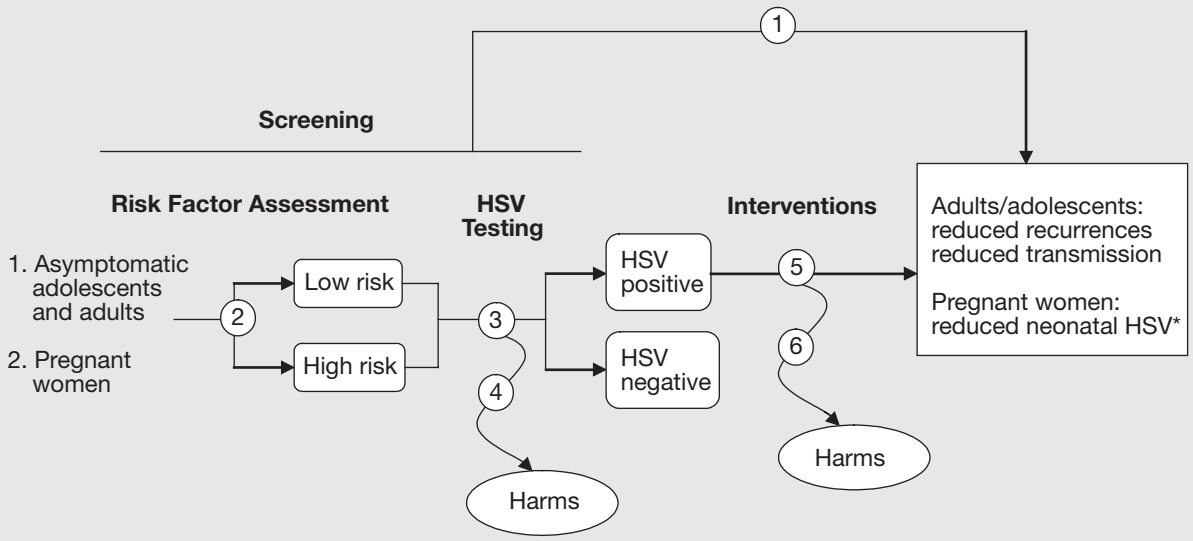
1b. Does screening for HSV in pregnant women reduce neonatal HSV and complications?

No studies were identified that directly evaluated whether screening asymptomatic pregnant women for genital HSV reduces neonatal HSV and complications.

A descriptive study of adult pregnant women (n = 1,355) with no previous history of genital HSV determined rates of genital HSV and asymptomatic HSV shedding in late pregnancy.[16] Participants were referred from 3 private obstetrics practices and were provided with education on signs and symptoms of genital HSV. HSV-2 antibody was detected in 32% of women with no clinical history of HSV. Asymptomatic HSV shedding was detected in late pregnancy and during delivery in 0.43%. Sixteen percent of seropositive women reported a first episode of clinical genital HSV during their pregnancy, demonstrating that education can assist asymptomatic, seropositive women in recognizing lesions.

A decision analysis estimated the benefit of serological screening in pregnancy by determining the number of cases of neonatal HSV-1 prevented by screening using models parameterized with data from published sources.[17] When screening pregnant women, a 90% specific/90% sensitive test for HSV-1 could avert 71% to 90% of the expected cases of infection, requiring about 14,000 tests per case averted. Screening pregnant women and their partners resulted in more tests for the same benefit

Figure. Screening for Genital Herpes: Analytic Framework and Key Questions



Key Questions

1a.	Does screening for HSV in asymptomatic adolescents and adults reduce symptomatic recurrences and transmission of disease?
1b.	Does screening for HSV in pregnant women reduce neonatal HSV and complications?
2.	Can risk factors identify groups at higher risk for HSV infection?
3a.	What are the HSV screening tests and their performance characteristics?
3b.	What is the optimal time to screen during pregnancy?
3c.	What is the role of screening partners?
4.	What are the harms of screening?
5a.	How effective are interventions in reducing symptomatic recurrences and transmission in adolescents and adults?
5b.	How effective are interventions in reducing neonatal infection and complications?
6.	What are the harms of interventions?

HSV, herpes simplex virus.
*Includes disseminated disease, encephalitis, neurological impairment, and death.

than screening only pregnant women (about 24,000 tests per case averted).

2. Can risk factors identify groups at higher risk for HSV infection?

No studies were identified that defined a set of risk factors and used them to guide selective serological screening for HSV-1 or HSV-2.

Four studies estimated the incidence and prevalence of HSV-1 and HSV-2 and examined associated factors for HSV infection.

A cross-sectional study examined the epidemiology of HSV-2 antibody and its suitability as a serological marker of sexual behavior in populations with high and low HSV-2 prevalence.[18] A sample of 869 adult patients attending a genitourinary medicine clinic and 1,494 consecutive adult blood donors were tested. Prevalence of HSV-2 antibody differed significantly between the groups: 22.7% in clinic participants and 7.6% in blood donor participants. In both groups, HSV-2 antibody was strongly associated with female gender, years of sexual activity, number of lifetime sexual partners, and past infection with STDs. Forty-five percent of those with HSV-2 antibody reported having symptoms suggestive of HSV infection, and only 27.4% had a previous diagnosis of HSV.

A cross-sectional study of a national sample indicated that at least 45 million adolescents and

adults aged 12 years and older, 1 out of 5, have had HSV-2 infections.[1] The seroprevalence of HSV-2 infection was 25.6% in women and 17.8% in men. Other independent predictors of HSV-2 infection included less education (defined by last year of education completed), poverty, cocaine use, and a greater lifetime number of sexual partners.

Seroprevalence rates based on HSV-2 results do not include the contribution of sexually acquired HSV-1. In a cross-sectional study, the characteristics of urban STD clinic patients who had HSV-1 were compared with those who had HSV-2.[3] Participants included 1,145 patients with positive genital HSV cultures treated from 1993–1997 with a mean age of 28 years. Participants defined themselves as heterosexual men (52 .4%), men who have sex with men (MSM) (7.9%), and heterosexual women (39.7%). Overall, 17.1% of cultures were positive for HSV-1 and 82.9% were positive for HSV-2. Of the 821 isolates from individuals with first-episode HSV infection, 20% had HSV-1. This compares with 9.9% of the 324 isolates with recurrent HSV infection. HSV-1 was found significantly more often in initial than in recurrent lesions (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.5–3.5). The proportion of isolates from initial lesions that were HSV-1 was greater for MSM (46.9%) than for women (21.4%), and was lowest for heterosexual men (14.6%). White race (OR, 3.7; 95% CI, 2.3–5.9) and receptive oral sex in the preceding 2 months (OR, 2.8; 95% CI, 1.9–4.3) significantly increased the odds that initial infections were HSV-1 rather than HSV-2. Age was not significantly associated with HSV-1 versus HSV-2 infection.

A prospective cohort study described incident cases of both HSV-1 and HSV-2 among HSV-2 seronegative sexually active participants.[19] Of the 2,393 HSV-2 seronegative participants, 1,508 were seropositive for HSV-1 at baseline. The rates of new HSV-1 and HSV-2 were 1.6 and 5.1 cases per 100 person-years respectively. Of the 155 new HSV-2 infections, 37% were symptomatic. Women participants were more likely than men to acquire HSV-2 ($P < 0.01$) and to have symptomatic infections. The higher rate of asymptomatic infection in men may be a factor in the higher rate of male to female HSV-2 transmission. Previous HSV-1 infection did not reduce the rate of HSV-2 infection, but it did increase the likelihood of asymptomatic seroconversion by a factor of 2.6 ($P < 0.001$). Of the 19 new cases of HSV-1 infections, 12 were symptomatic. The rates of symptomatic genital HSV-1 infection and oropharyngeal HSV-1 infection were the same (0.5 case per 100 person-years).

3a. What are the HSV screening tests and their performance characteristics?

New technologies include polymerase chain reaction (PCR) and glycoprotein G based, type-specific HSV serological tests.

A comparison of viral cell culture, direct antigen detection by HSV enzyme immunoassay (EIA), and PCR for diagnosis and typing of genital HSV was conducted in symptomatic adults. Of 194 patients, HSV was detected in 93 (48%) by viral cell culture, 76 (39%) by HSV EIA, and 115 (59%) by PCR. Comparison of the 3 methods indicated: 1) Viral cell culture vs PCR (sensitivity 93/115, 80.9%; specificity 79/79, 100%); 2) HSV EIA vs PCR (sensitivity 75/115, 65.2%; specificity 78/79, 98.7%); and 3) Viral cell culture vs HSV EIA (sensitivity 75/93, 80.7%; specificity 100/101, 99%).[20]

The frequency of asymptomatic HSV-2 viral shedding was determined by culture and PCR.[21] Thirteen HSV-2 seropositive pregnant women (9 completed the study) in prenatal care at a University clinic had daily genital tract samples collected during their third trimester for culture and PCR screening. Asymptomatic shedding was detected more frequently by PCR than by culture (13.8% vs 2.3%, $P < 0.0001$).

A comparison of the rate of isolation of HSV from viral culture with the rate of HSV DNA by PCR was examined in a study including both men and women.[22] Mucosal secretions (> 36,000 samples) from 296 HSV infected adults, enrolled in various studies from 1994–2001, were compared. Overall, HSV was isolated in 3% of samples and HSV DNA was detected in 12.1% of samples. The investigators reported a linear relationship between the ability to isolate viruses in the culture and the log number of copies of

HSV DNA in the sample. Importantly, this relationship persisted with men and women in HIV negative and HIV positive participant samples and on days when lesions were present or absent. The ratio of PCR positivity to viral culture positivity rose from 3.8:1.0 in the winter to 8.8:1.0 in the summer.

The FDA approved (1999–2000) the new glycoprotein G based, type-specific HSV serological tests for use in adults. Performance characteristics of commercial tests suggest that they are comparable to each other and to the gold standard Western blot assay for sensitivity and specificity (Table 1).[10,12,23,24] The commercial HerpeSelect® ELISA (enzyme-linked immunosorbent assay) and Immunoblot tests (Focus Technologies, Cypress, CA) can detect HSV-1 specific antibodies. However, no test can distinguish between HSV-1 antibodies that are generated in response to oral infection and those arising after a genital HSV-1 infection.[12] Type-specific tests for HSV-1 tend to be 5% to 10% less sensitive than their HSV-2 counterparts and may require more time for seroconversion to occur.

The accuracy of the Gull/Meridan ELISA test compared to the Western blot assay was assessed for 61 children aged 1 to 13 years (median age, 7.4 years).[25] The Gull/Meridian ELISA had a sensitivity of 100% for HSV-1 and specificities of 74% for HSV-1 and 48% for HSV-2; no patient in the sample (n = 61) was HSV-2 positive. When the Gull/Meridan test was removed from the market, the investigators extended the study to include 128 similarly aged patients (median age, 5.7 years) using the HerpeSelect ELISA test compared with Western blot assay. The HerpeSelect showed sensitivities of 80% for HSV-1 and 88% for HSV-2, and specificities of 97% for HSV-1 and 100% for HSV-2. The study did not provide age specific information regarding accuracy of HSV serological testing.

3b. What is the optimal time to screen during pregnancy?

We found no studies that evaluated the optimal time to screen during pregnancy.

3c. What is the role of screening partners?

We found no studies that evaluated screening partners.

4. What are the harms of screening?

A qualitative assessment of the psychosocial impact of receiving a serological diagnosis of HSV-2 in individuals without a previous history of infection was examined.[26] Investigators recruited 24 individuals who were seropositive for HSV-2 by Western blot assay and reported no clinical history of infection. Participants were recruited from clinical settings (STD, maternal and infant care, family medicine, and research clinics) over a 10-month period and completed an in-depth interview on their responses to 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, and relationship concerns relating to the diagnosis. Participants exhibited strong emotional and psychological responses to their serological diagnoses of HSV-2.

A descriptive study focused on physicians' skills in managing the potential psychological effects on parents when screening neonates for HSV.[27] The investigators conducted a series of semi-structured interviews with 15 physicians from 1 pediatric institution, and coded the resulting audiotapes for common themes. Themes included how physicians prepared families for screening and treatment, managed stigma, and perceived parental reactions. Techniques for fostering good communication included being direct and honest and ensuring that the time and place for discussion were appropriate.

Strategies for managing stigma associated with screening included placing the diagnosis in epidemiological context and discussing the potential severity of the disease.

5a. How effective are interventions in reducing symptomatic recurrences and transmission in adolescents and adults?

Antivirals to reduce HSV recurrences. Four randomized controlled trials (RCTs) (3 rated good-quality,[28–30] 1 rated fair-quality[31]) examined the effectiveness of antiviral agents in the suppression of HSV recurrences, and 1 good-quality RCT[32] evaluated the effectiveness of an antiviral agent in reducing subclinical viral shedding (Table 2).

A randomized, multicenter, multinational, double blind, placebo controlled trial assessed the effectiveness of oral famciclovir for suppression of recurrent HSV.[28] Eligible men and women (n = 455; 6 or more recurrences per year) were randomly assigned to receive 1 of 3 famciclovir regimens: 1) 125 mg 3 times daily; 2) 250 mg twice daily; or 3) 250 mg 3 times daily, or placebo for 52 weeks. In an intention-to-treat analysis, famciclovir significantly delayed the time to the first recurrence at all dose regimens compared with placebo ($P < 0.001$; hazard ratio [HR], 2.9–3.3; CI, 2.0–4.8). Median time to recurrence was 222 to 336 days for famciclovir groups compared with 47 days for the placebo group. The proportion of patients remaining free of HSV recurrence was significantly higher in the 3 treatment groups (79% to 86%) than in the placebo group (27%) at 6 months (relative risk [RR], 2.9–3.1; $P < 0.001$), and efficacy was maintained at 12 months. There was no reported difference in efficacy between the treatment regimens or between men and women. Famciclovir was well tolerated in all treatment groups with an adverse experience profile comparable to the placebo group.

A randomized, double blind, placebo controlled trial of famciclovir included women with recurrent genital HSV infections.[29] A total of 375 women with 6 or more recurrences per year were randomly assigned to 5 different famciclovir regimens: 1) 125 mg once daily; 2) 250 mg twice daily; 3) 250 mg once daily; 4) 250 mg twice daily; and 5) 500 mg once daily, or placebo and followed for 120 days. An intention-to-treat analysis indicated that the median time to first recurrence was significantly prolonged for those taking 125 mg of famciclovir twice daily (HR, 1.8; 95% CI, 1.0–3.0; $P = 0.03$) and 250 mg of famciclovir twice daily (HR, 3.6; 95% CI, 1.9–6.9; $P < 0.001$). The proportion of women who remained free of recurrences during the follow-up period was greatest with 250 mg of famciclovir twice daily (78%) compared with placebo (42%; $P < 0.001$). No significant differences were reported in the frequency and severity of clinical adverse experiences between the famciclovir and placebo groups.

Another randomized, multicenter, double blind, placebo controlled trial compared valacyclovir with placebo for the suppression of recurrent HSV.[31] Men and women (n = 382) with 8 or more recurrences per year were randomly assigned to receive either 500 mg oral valacyclovir once daily or a placebo for 16 weeks. Results indicated a significant difference in the time to first recurrence between the valacyclovir and placebo groups ($P < 0.0001$; HR, 0.16; 95% CI, 0.11–0.21). After the treatment period, 69% of the patients who received valacyclovir were recurrence free compared with 9.5% of the patients assigned to placebo. The safety of valacyclovir and placebo were comparable, with adverse experiences being infrequent and generally mild (eg, headache and nausea).

A randomized, double blind, placebo controlled trial compared the effectiveness in suppressing recurrent HSV using different valacyclovir regimens with placebo and acyclovir.[30] Men and women patients (n = 1,479) with 6 or more recurrences per year were randomly assigned to 4 different valacyclovir regimens: 1) 250 mg once daily; 2) 500 mg once daily; 3) 250 mg twice daily; or 4) 1,000 mg once daily, or 400 mg of acyclovir twice daily, or placebo. The patients were followed in all groups for 1 year. Seventy-one percent of patients completed the study. Results of an intention-to-treat analysis showed that all the antiviral regimens were effective in suppressing HSV recurrences compared with placebo ($P < 0.001$; HR, 0.21–0.46; CI, 0.16–0.59). The adverse experiences reported were similar for

Table 2. Trials of Suppressive Antiviral Therapy in Adults and Adolescents

Study/Year	N	Population	Antiviral/Dose	Design
Corey, 2004[33]	1,484 2 groups	Adult heterosexual monogamous couples (1 HSV seropositive partner and 1 HSV seronegative susceptible partner)	Oral valacyclovir 500 mg 1 time daily or placebo	DB RCT
Diaz-Mitoma, 1998[28]	455 4 groups	Adult males and females with history of 6 or more episodes of genital HSV in past 12–24 mos, in the absence of antiviral therapy	Oral famciclovir 125 mg or 250 mg 3 times a day, or 250 mg twice a day, or placebo	DB RCT, parallel groups
Reitano, 1998[30]	1,479 5 groups	Adult males and females with history of 6 or more episodes of genital HSV in past year	Oral valacyclovir 250 mg, 500 mg, or 1 g once daily, or 250 mg twice daily; oral acyclovir, 400 mg twice daily, or placebo	DB RCT

CI, confidence interval; DB, double blind; HR, hazard ratio; HSV, herpes simplex virus; PCR, polymerase chain reaction; RCT, randomized controlled trial; RR, relative risk.

Table 2. Trials of Suppressive Antiviral Therapy in Adults and Adolescents (cont)

Length of Trial	Main Outcomes/Results	Quality Rating/ Limitations
8 mos	1) Clinical symptoms of HSV-2 infection developed in 4/743 (0.5%) of treated partners compared to 16/741 (2.2%) of untreated partners (HR, 0.25; 95% CI, 0.08–0.75; $P = 0.008$); 2) HSV-2 was observed in 14 (1.9%) of treated partners compared with 27 (3.6%) untreated partners (HR, 0.52; 95% CI, 0.27–0.99; $P = 0.04$); 3) HSV DNA using PCR was detected in samples of genital secretions on 2.9% of the days among the HSV-2 treated partners compared with 10.8% of days among untreated partners ($P < 0.001$); 4) Viral shedding was detected in 48.7% of treated partners compared with 82% of untreated partners (RR, 0.60; 95% CI, 0.43–0.83; $P = 0.002$); 5) The lowest observed rates of transmission were among couples who reported almost always using condoms during intercourse and the source partner was taking once-daily valacyclovir; 6) The frequency of adverse effects was similar in both treatment and placebo groups.	Good
52 wks	1) Famciclovir significantly delayed the time to first recurrence at all dose regimens ($P < 0.001$); median time to recurrence was 222 to 336 days compared to 47 days for placebo group; 2) Proportion of patients remaining free of HSV recurrence; proportion 3 times higher in famciclovir group (79%–86%) than in placebo group (27%) at 6 mos; 3) Frequency of harms, safety profiles were comparable between groups.	Good
1 yr	1) Dose related response ($P < 0.0001$) across the 1 daily valacyclovir regimens; 2) Twice daily regimens of acyclovir and valacyclovir were similar in effectiveness; 3) 500 mg of valacyclovir once daily was most effective at managing patients with < 10 recurrences per year and 1 g of valacyclovir once daily, 250 mg of valacyclovir twice daily, or 400 mg of acyclovir twice daily were more effective in patients with > 10 recurrences per year. Safety profiles for all treatments were comparable.	Good

continue

Table 2. Trials of Suppressive Antiviral Therapy in Adults and Adolescents (cont)

Study/Year	N	Population	Antiviral/Dose	Design
Patel, 1997[31]	382 2 groups	Adult males and females with a history of 8 or more recurrences annually	Oral valacyclovir 500 mg once daily or placebo	DB RCT
Mertz, 1997[29]	375 6 groups	Adult women, 6 or more episodes of genital HSV during a 12–24 mo period	Oral famciclovir 125 mg once or twice daily, 250 mg once or twice daily, 500 mg once daily, or placebo	DB RCT
Wald, 1996[32]	34	Adult women with HSV-2 antibody and genital herpes of less than 2 yrs' duration	Oral acyclovir 400 mg twice daily for 70 days, 2 week washout, followed by 70 days of placebo, or reverse order	DB RCT, with crossover

each of the 4 valacyclovir groups, the acyclovir group, and the placebo group. Most adverse experiences reported by all groups were considered mild (eg, headaches, flu-like symptoms).

A randomized, double blind, placebo controlled, crossover trial assessed the use of acyclovir on the frequency of subclinical viral shedding in the genital tract.[32] Thirty-four eligible women (HSV-2 antibody only and genital HSV of less than 2 years' duration) were randomly assigned to receive either acyclovir (400 mg daily) for 70 days, followed by a 2 week washout period, and then followed by placebo for 70 days, or the study protocol in the reverse order. In an intention-to-treat analysis, 88% (15/17) of women who received placebo and 18% (3/17) who received acyclovir had at least 1 day of subclinical viral shedding ($P < 0.001$). The relative risk for subclinical viral shedding was 0.09 (95% CI, 0.03–0.35) for the women who received acyclovir compared with the women who received placebo.

Antivirals to reduce HSV transmission. A good-quality, randomized, multicenter, double blind, placebo controlled trial was conducted to determine the effectiveness of once-daily valacyclovir to reduce sexual transmission of genital HSV (Table 2).[33] Eligible healthy, monogamous, heterosexual couples (n = 1,484 at 96 centers) were discordant for HSV-2 infection. The source partner was aged 18 or older, had recurrent HSV-2 with fewer than 10 episodes per year, and did not use daily antiviral therapy. The susceptible partner was aged 18 or older and HSV-2 seronegative on Western blot assay.

Couples were randomly assigned to receive either 500 mg of valacyclovir once daily or placebo for 8 months. The susceptible partner was evaluated monthly for clinical signs and symptoms of genital

Table 2. Trials of Suppressive Antiviral Therapy in Adults and Adolescents (cont)

Length of Trial	Main Outcomes/Results	Quality Rating/ Limitations
16 wks	1) First recurrence; significant difference was found between valacyclovir and placebo in the time to 1st recurrence ($P < 0.0001$); 2) Efficacy of valacyclovir; valacyclovir prevented or delayed 85% of the recurrences and at 16 wks, 69% of treatment group were recurrence free and 9.5% of placebo group were recurrence free; 3) Safety profiles were comparable between groups.	Fair
4 mos	1) Time to 1st recurrence of genital HSV, significantly prolonged in patients who received famciclovir, 125 mg twice daily ($P = 0.03$), and in those who received famciclovir 250 mg twice daily ($P < 0.001$); 2) Safety profiles between groups were comparable.	Good
140 days	1) Frequency of subclinical viral shedding in genital tract; 15/17 women who received placebo and 3/17 women who received acyclovir had at least 1 day of subclinical shedding ($P < 0.001$); 2) Subclinical shedding occurred on 6.9% of days in placebo women and 0.3% of days in treatment women ($P < 0.001$); 3) Acyclovir resulted in a 94% reduction in viral shedding among the 26 women who completed both arms of the study.	Good/single research clinic site

HSV, and the source partner was followed for recurrence of genital HSV. Both partners received counseling on safer sex and were offered condoms at each visit. The study endpoint was the reduction in transmission of symptomatic genital herpes.

Clinical symptoms of HSV-2 infection developed in 4/743 (0.5%) susceptible partners who were given valacyclovir compared with 16/741 (2.2%) susceptible partners who were given placebo (HR, 0.25; 95% CI, 0.08–0.75; $P = 0.008$). Acquisition of HSV-2 was observed in 14 (1.9%) susceptible partners who received valacyclovir compared with 27 (3.6%) who received placebo (HR, 0.52; 95% CI, 0.27–0.99; $P = 0.04$). HSV DNA using PCR was detected in samples of genital secretions on 2.9% of the days among the HSV-2 source partners who received valacyclovir, compared with 10.8% of days among those source partners who received placebo ($P < 0.001$). Viral shedding was detected in 48.7% of source partners who received valacyclovir compared with 82% of source partners who received placebo (RR, 0.60; 95% CI, 0.43–0.83; $P = 0.002$).

After counseling, 37% of the couples reported at each monthly visit that they never used condoms for vaginal or anal intercourse during the study. Covariate analyses, accounting for reported use of condoms during the study, indicated that once-daily valacyclovir use continued to be associated with reduced rates of transmission. The lowest observed rates of transmission were among couples who reported almost always using condoms during intercourse, and the source partner was taking once-daily valacyclovir. The frequency of harms was similar in the valacyclovir and placebo groups.

Condom use to reduce HSV transmission. A prospective cohort study suggested that male condom use may decrease the risk for sexual

transmission of HSV-2 among women who have a sexual partner discordant for HSV-2.[34] In the study, 528 monogamous couples discordant for HSV-2 infection (261 susceptible men and 267 susceptible women) were followed for 18 months. The findings suggested that male condom use in 25% of episodes of sexual intercourse was associated with a lower risk for HSV-2 acquisition among women (adjusted HR, 0.09; 95% CI, 0.01–0.67) but not for men (adjusted HR, 2.02; 95% CI, 0.32–12.50). Condom use was low throughout the study; only 61% of the couples reported ever using condoms and only 8% reported condom use for each sexual act, despite counseling at each clinic follow-up visit.

The efficacy of condom use against HSV-2 transmission was evaluated in a prospective cohort study of adult men and women attending STD clinics.[35] A cohort of 1,862 HSV-2 susceptible persons with 4 or more sexual partners, or 1 or more STDs in the past year, was followed for 18 months. One hundred and eighteen (6.4%) persons acquired HSV-2, for an overall rate of 5.2/100 person-years. The rates for women and men were similar (5.7 vs 5.1/100 person-years). In multivariate models, frequency of sexual activity (HR, 1.11; 95% CI, 1.04–1.2) and an STD in the year prior to the study (HR, 1.31; 95% CI, 1.01–1.71) were associated with increased risk for HSV-2. Use of condoms for more than 65% of sex acts offered significant protection against HSV-2 acquisition for men (HR, 0.56; 95% CI, 0.33–0.97), as well as for the total population (HR, 0.58; 95% CI, 0.37–0.92). The degree of protection was comparable in women (HR, 0.66; 95% CI, 0.30–1.46), heterosexual men (HR, 0.59; 95% CI, 0.32–1.08), and MSM (HR, 0.42; 95% CI, 0.12–1.49).

Vaccines. Vaccines to prevent genital HSV have not been approved by the FDA, and vaccine trials are ongoing. Four RCTs conducted by 2 investigative groups examined the efficacy of HSV-2 vaccines for the prevention of genital HSV.[36,37] Additionally, 3 RCTs examined the efficacy of vaccine in the treatment of recurrent genital HSV.[38–40] All of the RCTs are testing different forms of vaccine.

Vaccines to prevent HSV. Two randomized, multinational, double blind, placebo controlled trials of an HSV-2 glycoprotein-D adjuvant vaccine were conducted in patients whose regular sexual partners had a history of genital HSV.[36] In study 1, eligible patients (n = 847; 268 women) were seronegative for HSV-1 and HSV-2. In study 2, eligible patients (n = 1,867; 710 women) were of any serological status. Patients received vaccine or control injections at 0, 1, and 6 months, and were then followed for 19 months. The endpoints of the studies were occurrence of genital HSV disease in the patients in study 1 and in seronegative women patients in study 2. Intention-to-treat analysis indicated efficacy of 38% (95% CI, 18% to 68%) in study 1 and 42% (95% CI, 31% to 74%) for women patients in study 2. In the post-hoc subgroup analysis, the vaccine provided higher levels of protection in women but not in men. The vaccine efficacy was 73% (95% CI, 9% to 91%; $P = 0.01$) in women who were seronegative for both HSV-1 and HSV-2 at baseline in study 1. In study 2, the efficacy for women was 74% (95% CI, 9% to 93%; $P = 0.02$). The vaccine was not efficacious in women who were seropositive for HSV-1 and seronegative for HSV-2 at baseline or in men regardless of their HSV serological status. The vaccine was generally well tolerated. The majority of doses of vaccine were followed by soreness at site of injection, and most symptoms reported were mild to moderate.

Two additional randomized, multicenter, double blind, placebo controlled trials of a recombinant glycoprotein vaccine for prevention of HSV-2 infection were also reported.[37] A total of 2,268 eligible patients (seronegative for HSV, seronegative partners of HSV infected persons and persons attending an STD clinic) were randomized to placebo or vaccine groups. The patients were followed for up to 1 year after 3 vaccine administrations. The study outcomes were time to HSV acquisition during the study period. Overall vaccine efficacy was 9% (95% CI, –29% to 36%). The vaccine induced high levels of HSV-2 specific antibodies in vaccinated persons who did and did not develop genital HSV. The vaccine was safe and well tolerated.

Vaccines to treat recurrent HSV. A randomized, double blind, placebo controlled trial evaluated the Skinner vaccine for the

treatment of recurrent genital herpes.[38] Eligible patients (n = 316 with 6 or more genital HSV recurrences per year) were randomly assigned to receive vaccination or a placebo at 0, 1, and 2 months. Recurrence severity was significantly reduced in the intervention group ($P = 0.04$). The frequency of recurrences was reduced in the vaccinated women patients at both 3- and 6-month follow-up. Overall recurrence reduction for both men and women after 6 months did not reach statistical difference. There were no serious systemic or local adverse reactions to the vaccination.

A randomized, double blind, placebo controlled trial was conducted to examine the efficacy of a recombinant HSV-2 glycoprotein D and B vaccine in the treatment of recurrent genital herpes.[39] Eligible participants (n = 202; 4–14 recurrences per year) were randomly assigned to HSV vaccine or a placebo injection at 0, 2, 12, and 14 months, and followed up at 18 months. The duration and severity of the first clinically confirmed outbreak after vaccination was significantly reduced in the vaccination group ($P = 0.003$ for differences in severity; $P = 0.002$ for differences in duration). However, the monthly rate of recurrences was not significantly improved in the vaccine group. Adverse experiences were generally mild to moderate but statistically higher after each vaccination compared with the placebo injection ($P < 0.01$).

A randomized, double blind, placebo controlled trial evaluated a recombinant glycoprotein-D vaccine for recurrent HSV-2.[40] Eligible patients (n = 98, 4–14 recurrences per year and free from genital lesions) were randomly assigned to vaccine or placebo injection at baseline, and after 2 months, and followed up at 1 year. The vaccine group experienced a lower median number of clinically and virologically confirmed recurrences than the placebo group (3 vs 4; $P = 0.025$). Time to first genital HSV recurrence was not significantly different by group. Adverse experiences were reported frequently (100% vaccine groups and 90% of placebo group) but typically mild (eg, headaches, chills, nausea).

5b. How effective are interventions in reducing neonatal infection and complications?

Antivirals to suppress HSV recurrences in late pregnancy. A recently published systematic review and meta-analysis of RCTs of acyclovir prophylaxis during late pregnancy included 5 trials enrolling a total of 799 women with prior HSV infections.[41] A fixed-effects model was used to calculate a summary odds ratio comparing the effect of treatment with placebo. Prophylactic acyclovir beginning at 36 weeks' gestation reduced the risk for clinical HSV recurrence at delivery (OR, 0.25; 95% CI, 0.15–0.40), cesarean delivery for recurrent HSV (OR, 0.30; 95% CI, 0.13–0.67), and HSV shedding at delivery (OR, 0.09; 95% CI, 0.02–0.39). None of the published studies had adequate power to address the effect of prophylactic acyclovir on neonatal HSV, and no neonatal HSV infections were reported. All of the RCTs included in the meta-analysis were published since the prior USPSTF recommendation on screening for genital herpes and are included in this update (Table 3).[42–46]

A good-quality, randomized, double blind, placebo controlled trial was conducted to assess the efficacy of acyclovir in the reduction of HSV recurrences and cesarean delivery.[42] Eligible women (n = 162, pregnant women with at least 1 symptomatic episode of genital HSV during pregnancy or the year before pregnancy) were randomly assigned to acyclovir (400 mg 3 times daily) or identical placebo after 36 weeks' gestation. Patients identified clinical lesions and collected HSV cultures and DNA PCR samples. Five percent of patients treated with acyclovir and 14% of patients treated with placebo had HSV lesions at delivery ($P = 0.08$). HSV culture and PCR positivity near delivery occurred in 7% and 34% of women in the placebo group and 0% and 2% in the acyclovir group ($P = 0.03$ and $P < 0.01$ respectively). Four percent of women in the acyclovir group delivered by cesarean compared with 10% in the placebo group ($P = 0.17$). Six percent of the women in the study had persistent detection of HSV by PCR more than 20% of the days, despite reporting taking 90% to 100% of the acyclovir doses. Neonatal outcomes were similar between groups, and the study did not examine neonatal safety.

Table 3. Trials of Suppressive Antiviral Therapy in Pregnant Women

Study/Year	N	Population	Antiviral/Dose	Design
Watts, 2003[42]	162 2 groups	Adult women with recurrent genital HSV at gestational age < 36 wks	Oral acyclovir 400 mg 3 times daily or placebo	DB RCT
Scott, 2002[43]	234 2 groups	Adult women with recurrent genital HSV at gestational age < 36 wks	Oral acyclovir 400 mg 3 times daily or placebo	DB RCT
Scott, 2001[47]	96	Adult women with first diagnosis of genital HSV in index pregnancy, 36 wks' gestation	Oral acyclovir 400 mg 3 times daily	Open-label trial with historical controls

CI, confidence interval; DB, double blind; HSV, herpes simplex virus; OR, odds ratio; PCR, polymerase chain reaction; RCT, randomized controlled trial.

A fair-quality, randomized, double blind, placebo controlled trial was conducted to evaluate the use of suppressive acyclovir near term to decrease the frequency of clinical recurrences at delivery in women with recurrent genital HSV infection.[43] Eligible women (n = 234 women with any frequency of recurrent HSV) were randomly assigned to either oral acyclovir (400 mg 3 times daily) or an identical placebo after 36 weeks' gestation. Clinical lesions were identified, and HSV cultures were obtained at delivery. Six percent of patients treated with acyclovir and 14% of patients treated with placebo had clinical HSV at delivery ($P = 0.046$). No patients in the acyclovir group had positive HSV cultures compared with 6% in the placebo group ($P = 0.029$). There was no significant difference in subclinical HSV shedding in the acyclovir group (0%) compared with the placebo group (3%; $P = 0.102$). The study was not

Table 3. Trials of Suppressive Antiviral Therapy in Pregnant Women (cont)

Length of Trial	Main Outcomes/Results	Quality Rating/ Limitations
36 wks' gestation to delivery	1) 5% of patients treated with acyclovir, and 14% of patients treated with placebo had HSV lesions at delivery ($P = 0.08$); 2) 7% in the acyclovir group had positive HSV cultures and PCR, compared with 34% of placebo-treated patients ($P = 0.03$ and < 0.01 respectively); 3) 4% of women in the acyclovir group delivered by cesarean, and 10% of women in the placebo group delivered by cesarean ($P = 0.17$); 4) Neonatal outcomes were similar between groups; 5) Importantly, 6% of the women in the study had persistent detection of HSV by PCR on > 20% of days, despite reporting taking 90%–100% of the acyclovir doses; 6) The study did not examine safety of the neonate.	Good
36 wks' gestation to delivery	1) Decreased frequency of clinical recurrences, 6% of treatment and 14% of placebo group had clinical HSV at delivery ($P = 0.046$); 2) No women had positive HSV cultures in treatment group compared with 6% positives in placebo group ($P = 0.029$); 3) No significant difference in subclinical HSV shedding in the treatment group compared with placebo group; 4) The study did not examine safety of the neonate.	Fair/loss to follow-up not reported
36 wks' gestation to delivery	1) 85% of patients adhered to treatment, 1% had clinical HSV at delivery; 2) 4% of the cohort had clinical recurrences compared with 18%–37% of historical controls; 3) Asymptomatic shedding occurred in 1% of women without lesions at delivery; 4) No harms (neurological, hepatic, renal complications) were attributable to acyclovir during the neonatal period.	Poor/not randomized or blinded, groups not similar at baseline, and comparable groups not maintained

continue

designed to evaluate the safety of suppressive acyclovir on the fetus.

A poor-quality, randomized, double blind, placebo controlled trial was conducted to evaluate the efficacy of suppressive acyclovir in late pregnancy to prevent recurrent genital HSV.[44] Eligible women (n = 63) with recurrent HSV infection under 36 weeks' gestation were randomly assigned to acyclovir (200 mg 4 times daily) or placebo from 36 weeks' gestation until the time of delivery. Women were followed weekly, and viral cultures were obtained from the cervix and vulva. No specific instructions were set up for obstetrical management. The proportion of women undergoing cesarean delivery for recurrent HSV at delivery was 19% (n = 12). The odds ratio for clinical HSV recurrence was significantly reduced in the treatment group (0.10; 95% CI, 0.00–0.86). Odds ratios for cesarean deliveries (0.44; 95% CI,

Table 3. Trials of Suppressive Antiviral Therapy in Pregnant Women (cont)

Study/Year	N	Population	Antiviral/Dose	Design
Braig, 2001[46]	489 3 groups	Adult women with at least 1 episode of genital HSV at gestational age < 36 wks	Group 1 (n = 167) received oral acyclovir 200 mg 4 times daily; Group 2 (n = 121) received no treatment; Group 3 (n = 201), historical controls, women not given prophylaxis who had a history of genital HSV	RCT with historical controls (Group 3)
Brocklehurst, 1998[44]	63 2 groups	Adult women with recurrent genital HSV at gestational age < 36 wks	Oral acyclovir 200 mg 4 times daily or placebo	DB RCT
Scott, 1996[45]	46 2 groups	Adult women with recurrent genital HSV at gestational age < 36 wks	Oral acyclovir 400 mg 3 times daily or placebo	DB RCT

0.09–1.59) and asymptomatic shedding during treatment (0.32; 95% CI, 0.05–1.56) were not statistically significantly reduced among women in the treatment group. No information was reported on adverse experiences.

A poor-quality, randomized, double blind, placebo controlled trial was conducted to determine the efficacy of acyclovir suppressive therapy to prevent cesarean delivery after a first episode of genital HSV.[45] Eligible women (n = 46) with first episodes of HSV during pregnancy were randomly assigned to oral acyclovir (400 mg 3 times daily) or placebo. The study was conducted from 36 weeks' gestation to delivery, and HSV cultures were obtained at delivery. In an intention-to-treat analysis, none of the women treated with acyclovir had clinical evidence of recurrent HSV at delivery compared with 9 women taking placebo (OR, 0.04; 95% CI, 0.002–0.75; $P = 0.002$). Overall, 4 of 21 women in the treatment group had cesarean deliveries (none related to HSV lesions), compared with 10 of 25 women in the placebo group (OR, 0.35; 95% CI, 0.07–1.59; $P = 0.22$). No patient in either group experienced asymptomatic viral shedding, and no infant in either group had clinical or virological evidence of HSV infection. No adverse experiences related to acyclovir treatment in neonates were reported at 1-month follow-up.

A poor-quality, open-label trial evaluated the use of antiviral suppression after a first episode of

Table 3. Trials of Suppressive Antiviral Therapy in Pregnant Women (cont)

Length of Trial	Main Outcomes/Results	Quality Rating/ Limitations
36 wks' gestation to delivery	1) The rate of cesarean delivery was 8.4% in treatment group (Group 1), 16.5% in no treatment group (Group 2), and 9.9% in historical controls (Group 3) ($P < 0.001$); 2) 75% of cesarean deliveries in Group 2 and 10% of cesarean deliveries in Group 3 were done because of genital HSV; 3) Percentage of viral shedding was 0% in Group 1, 5% in Group 2, and 0.5% in Group 3; 4) No neonatal herpes were diagnosed during the study period and no harms for the newborn related to antiviral therapy were reported.	Poor/not randomized or blinded, not intention-to-treat, maintenance of comparable groups not reported
36 wks' gestation to delivery	1) The number of clinical recurrences of genital HSV was significantly reduced in the treatment group compared with placebo (OR, 0.10; 95% CI, 0.00–0.86); 2) This trial did not demonstrate that acyclovir use in late pregnancy reduced cesarean delivery; 3) No HSV among neonates were reported, and no adverse complications were reported for the infants at 1-yr follow-up.	Poor/groups not similar at baseline, not blinded, maintenance of comparable groups not reported, loss to follow-up not reported
36 wks' gestation to delivery	1) None of the treatment group and 35% of the placebo group had clinical evidence of recurrent genital HSV at delivery (OR, 0.04; 95% CI, 0.002–0.745; $P = 0.002$); 2) Women treated with acyclovir had no cesareans for genital herpes compared with 36% of placebo group (OR, 0.04; 95% CI, 0.002–0.745; $P = 0.002$); 3) No neonates had evidence of herpes infection or harms from acyclovir.	Poor/not intention-to-treat analysis, maintenance of comparable groups and loss to follow-up not reported

genital HSV infection in late pregnancy.[47] Eligible women (n = 96) diagnosed with genital herpes for the first time in the index pregnancy were prescribed 400 mg of suppressive acyclovir orally 3 times daily from 36 weeks' gestation until delivery. Herpes cultures were obtained when patients presented for delivery. Vaginal delivery was permitted if no clinical recurrence was present; otherwise, a cesarean delivery was performed. Neonatal HSV cultures were obtained, and infants were followed clinically. In 82 patients (85%) adherent with therapy, only 1% had clinical HSV recurrences at delivery. In an intention-to-treat analysis of the entire cohort, 4% had clinical recurrences (compared with 18% to 37% in historical controls). Asymptomatic shedding occurred in 1% of women without lesions at delivery. Two of the 4 clinical recurrences were HSV-culture positive. No significant maternal or fetal side effects were observed.

Antivirals to reduce viral shedding in late pregnancy. Limited evidence exists on the use of antiviral therapy to reduce viral shedding and therefore reduce transmission of HSV to neonates. A poor-quality randomized trial was conducted to investigate the use of acyclovir prophylaxis in late pregnancy to reduce the risk for viral shedding and mother-to-child transmission at delivery.[46] Eligible women (n = 288, at least 1 episode of genital HSV during pregnancy) were randomly assigned to 2 groups: group 1 (n = 167) received

oral acyclovir from 36 weeks' gestation to term; group 2 (n = 121) received no treatment. Group 3 (n = 201) comprised women who were not given prophylaxis, had a history of genital herpes, and had no active episodes during pregnancy. No specific instructions were set up for obstetrical management except for cesarean delivery in case of suspected herpes lesions at the time of labor. The rate of cesarean delivery was 8.4% in group 1, 16.5% in group 2, and 9.9% in group 3 ($P < 0.001$). Seventy-five percent of cesarean deliveries in group 2 and 10% in group 3 were done because of genital HSV. The percentage of viral shedding was, respectively, 0% in group 1, 5% in group 2, and 0.5% in group 3 ($P < 0.05$). The study did not report information on adverse experiences.

Cesarean delivery to reduce HSV transmission. A prospective cohort study was designed to demonstrate prevention of transmission of HSV to neonates by using cesarean delivery—a common practice for 30 years.[48] The study enrolled 58,362 pregnant women between January 1982 and December 1999 at a university medical center, a U.S. Army medical center, and 5 community hospitals in Washington State. Of these, 40,023 had HSV cultures obtained from the cervix and external genitalia, and 31,663 had serum samples tested for HSV twice. Among the 202 women HSV positive at the time of labor, 10 (5%) had neonates with HSV infection (OR, 346; 95% CI, 125–956 for neonatal herpes when HSV was isolated vs not isolated). There was 1 case of neonatal herpes among 85 cesarean deliveries vs 9 cases (7.7%) among 117 vaginal deliveries (OR, 0.14; 95% CI, 0.02–1.08; $P = 0.047$).

While the investigators concluded that cesarean delivery reduces the risk for HSV transmission, this conclusion is not supported for the following reasons:

- Although a *P*-value of 0.047 is given, the confidence interval for the odds ratio crosses 1. The *P*-value was calculated by Fishers exact test, while the confidence interval for the odds ratio was calculated by logistic regression. When the odds ratio was adjusted for first-episode vs reactivation, the confidence interval was even wider (0.02–1.26), and the odds ratio was not statistically significant.
- Results of observational studies of surgical effectiveness do not always predict the results of controlled trials, and no controlled trials of cesarean section to prevent neonatal HSV transmission have been conducted.
- Cesarean section and vaginal delivery were used for different patient subgroups in the cohort. In the study sub-analysis of 177 women who had HSV antibody tests, as well as positive cultures at term, 56 of the 68 cesareans were done in subgroups of women who had no cases of neonatal transmission regardless of delivery method. Fifty cesareans were done in women who had reactivation of previous HSV-2 infection (a group that had no neonatal transmission regardless of delivery method). Conversely, there were only 3 cesarean sections among the 15 HSV-1 infected women (a group that accounted for half of the cases of neonatal herpes). The authors attributed the high rate of transmission in HSV-1 infected women to the fact that cesarean section was not frequently used. While this interpretation may be correct, the study does not provide direct data to support it.
- In the highest-risk subgroup of HSV-2 positive women (non-primary, first-episode HSV-2 infections without lesions at delivery) the rates of transmission were not substantially different for cesarean delivery (1/4) and vaginal delivery (3/11).

6. What are the harms of interventions?

There is limited evidence on the safety of antiviral treatments during pregnancy. A prospective, double-blind, phase 1 trial evaluated the pharmacokinetics and safety of valacyclovir and acyclovir during pregnancy.[49] Eligible women (n = 20) with a history of recurrent genital HSV infections and positive HSV-2 serologies were randomly assigned at 36 weeks' gestation to oral valacyclovir (500 mg twice daily) or acyclovir (400 mg 3 times daily). Pharmacokinetic profiles were obtained after the initial dose (36 weeks' gestation) and at steady state (38 weeks' gestation).

Amniotic fluid samples were obtained during labor, and simultaneous umbilical cord and maternal plasma samples were collected at delivery. Laboratory studies were performed to screen for evidence of toxicity in mothers and infants. There was no significant difference in drug elimination half-life or in time to peak concentration between valacyclovir and acyclovir recipients at either sampling interval. Acyclovir was more highly concentrated in the amniotic fluid, but there was no evidence of preferential fetal drug accumulation (mean maternal/umbilical vein plasma ratios at delivery were 1.7 for valacyclovir and 1.3 for acyclovir). Drugs were well tolerated, and no significant laboratory or clinical evidence of toxicity was detected. Maternal valacyclovir therapy resulted in higher plasma levels, with significantly higher peak concentrations, and daily area under the curve values, than acyclovir therapy.

The acyclovir and valacyclovir pregnancy registry is maintained by GlaxoSmithKline and provides information on harms.[50] Both acyclovir and valacyclovir have been designated pregnancy category B by the Food and Drug Administration (FDA) and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Findings from the acyclovir registry did not show an increase in the number of birth defects when compared with the general population. Reported defects showed no uniqueness or pattern to suggest a common etiology. However, data from reported cases do not represent a sufficient sample size for reaching reliable and definitive conclusions regarding the risk for acyclovir to pregnant women and their developing fetuses. Similarly, the data for prenatal exposure to valacyclovir were too limited to provide useful information on pregnancy outcomes.

Cost Analyses

Acyclovir in Late Pregnancy

A cost analysis of oral acyclovir prophylaxis in late pregnancy (acyclovir and cesarean delivery when HSV lesions were present or acyclovir and follow-up of infants exposed to HSV lesions at delivery) was compared with the current standard of cesarean delivery for genital HSV lesions.[51] Clinical outcomes and direct costs of prevention were evaluated using decision analysis. Probabilities were obtained from the literature and experts. Cost data were based on hospital costs and costs of caring for HSV infected neonates. Without prophylactic acyclovir, an estimated 1,082 cesarean deliveries would be performed to prevent 2.8 cases of neonatal HSV in a cohort of 10,000 women. Costs include $1,319,457 per case of neonatal HSV prevented, and $3,012,459 per death or disability prevented. Using prophylactic acyclovir, the rate of cesarean deliveries would be reduced to 216 per 10,000 women, preventing 5.5 neonatal HSV infections. Costs include $493,641 per case prevented, and $1,127,034 per death or disability prevented. Prophylactic acyclovir and follow-up of infants exposed to HSV at delivery without performing cesarean deliveries would prevent 5 cases of neonatal HSV infections at a cost of $400,382 per case prevented, and $914,114 per death or disability prevented.

Another cost analysis compared use of acyclovir suppressive therapy to prevent recurrent genital HSV at delivery to no medical treatment.[52] Estimates of risk for HSV recurrence and cesarean delivery rates (in acyclovir treated and untreated patients) and frequency of neonatal acyclovir treatment were derived from literature reviews and experts. Using these data, the average obstetrical cost per patient not treated with acyclovir was estimated as $7,625. The average obstetrical cost per patient treated with acyclovir during the last weeks of pregnancy was estimated as $7,442.

Effectiveness, cost, and benefit of suppressive therapy among HSV serodiscordant sex partners during pregnancy was assessed.[53] Decision and economic analyses were used to compare the incidence and costs of neonatal herpes in California (2000) for 3 interventions: 1) no management; 2) current guidelines (cesarean delivery for women with lesions); and 3) screening for women at risk and use of suppressive treatment in sex partners. Screening and suppressive therapy was the most effective strategy. Current guidelines had limited effectiveness, but were cost saving. A potential 82% decrease in neonatal herpes incidence would be

possible with screening and suppressive therapy, but would cost $363,000 per case prevented.

Maternal Type-Specific HSV to Prevent Neonatal HSV Infection

Investigators performed a decision analysis model to test the value of routine HSV serology in pregnancy to prevent neonatal HSV infection.[54] Hypothetically, if one million pregnant women were screened, the rate of neonatal HSV-1 transmission would be marginally reduced from 126 to 99, and the rate of neonatal HSV-2 infection would be reduced from 157 to 124. The cost per serious case of neonatal HSV averted would be $891,000.

Conclusions

A summary of evidence considered for this update is described in Table 4.

At this time, no professional health organizations recommend routine screening for genital HSV in asymptomatic adolescents and adults.

The American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention recommend against surveillance viral cultures for HSV in asymptomatic pregnant women.[13,55] Rather, they recommend that all pregnant women be asked about a history of genital HSV early in the pregnancy and that they be carefully questioned about HSV symptoms and examined for genital lesions at the time of delivery. Women without known genital HSV should be counseled to avoid exposure during the third trimester with known or suspected HSV-1 or HSV-2 infection.

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Table 4. Summary of Evidence

Key Questions	New Evidence
1a. Does screening for HSV in asymptomatic adolescents and adults reduce symptomatic recurrences and transmission of disease?	No studies evaluated this question.
1b. Does screening for HSV in pregnant women reduce neonatal HSV and complications?	No studies evaluated this question.
2. Can risk factors identify groups at higher risk for HSV infection?	No studies evaluated this question.
3a. What are the HSV screening tests and their performance characteristics?	New technologies include polymerase chain reaction (PCR) and glycoprotein-G based, type-specific HSV serological tests; 2 type-specific HSV serological tests have been FDA approved and are available commercially; all have sensitivity and specificity consistent with the "gold standard" screening test (Western Blot Assay); PCR is more sensitive than viral cell culture and is the "gold standard" for diagnosing CNS HSV infection.
3b. What is the optimal time to screen during pregnancy?	No studies evaluated this question.
3c. What is the role of screening partners?	No studies evaluated this question.
4. What are the harms of screening?	A qualitative assessment of the psychosocial impact of a serological diagnosis of HSV-2 in individuals without a previous history of infection included strong emotional and psychological responses.
5a. How effective are interventions in reducing symptomatic recurrences and transmission in adolescents and adults?	Once-daily valacyclovir reduces sexual transmission of genital HSV in heterosexual monogamous couples; different antiviral agents and doses effectively suppress HSV recurrences compared with placebo; the safety of antivirals and placebo were comparable in trials and adverse experiences were reported as infrequent and generally mild (eg, headache and nausea); condoms provide partial prevention of sexual HSV transmission for both men and women; vaccines are not effective in preventing or reducing transmission of genital HSV.
5b. How effective are interventions in reducing neonatal infection and complications?	Antiviral use in late pregnancy reduces HSV recurrence and viral shedding; its effect on neonatal infections has not been determined.
6. What are the harms of interventions?	A pregnancy registry of antivirals indicated no increase in birth defects; no data on harms were identified.

CNS, central nervous system; FDA, Food and Drug Administration; HSV, herpes simplex virus.

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Appendix

Appendix 1. Search Strategies

Database: MEDLINE®

Dates: 1996 to March 2004

Asymptomatic adolescents and adults

1 exp Herpes Genitalis/ or genital herpes simplex.mp.

2 exp herpesvirus 1, human/ or exp herpesvirus 2, human/

3 limit 2 to all infant <birth to 23 months>

4 1 or 3

5 limit 4 to (human and English language and all infant <birth to 23 months> and [clinical trial or guideline or meta analysis or multicenter study or practice guideline or review])

6 limit 5 to yr=1996–2002

Pregnant women

1 exp Herpes Genitalis/ or genital herpes simplex.mp.

2 exp herpesvirus 1, human/ or exp herpesvirus 2, human/

3 screen$.mp. or exp mass screening/

4 (1 or 2) and 3

5 exp pregnancy/ or exp pregnancy complications/ or exp infant/ or fetus.mp. or fetal.mp. or disease transmission, vertical/

6 4 and 5

7 limit 6 to (human and English language and yr=1996–2002)

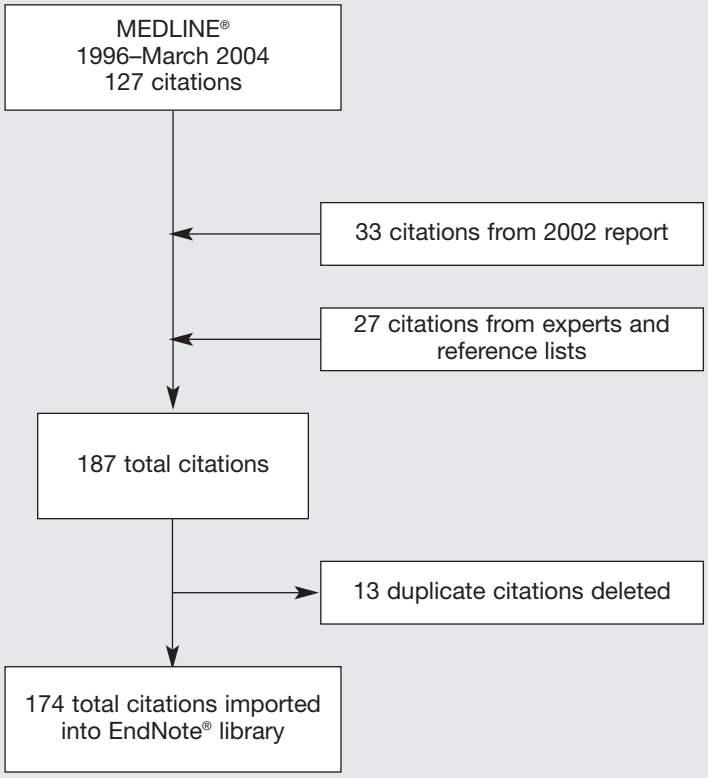
Appendix 2. Quality Ratings for Studies on Antiviral Therapy

Study/Year	Random Assignment?	Allocation Concealed?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Blinding: Outcome Assessors, Care Provider, Patient?	Intention-to-Treat Analysis?
Adults and Adolescents						
Corey, 2004[33]	Yes	Yes	Yes	Yes	Yes	Yes
Diaz-Mitoma, 1998[28]	Yes	Yes	Yes	Yes	Yes	Yes
Reitano, 1998[30]	Yes	Yes	Yes	Yes	Yes	Yes
Patel, 1997[31]	Yes	Yes	Yes	Yes	Yes	Yes
Mertz, 1997[29]	Yes	Yes	Yes	Yes	Yes	Yes
Wald, 1996[32]	Yes	Yes	Yes	Yes	Yes	Yes
Pregnant Women						
Watts, 2003[42]	Yes	Yes	Yes	Yes	Yes	NR
Scott, 2002[43]	Yes	Yes	Yes	Yes	Yes	Yes
Braig, 2001[46]	No	No	Yes	Yes	No	No
Scott, 2001[47]	No	No	No	Yes	No	Yes
Brocklehurst, 1998[44]	Yes	Yes	No	Yes	No	Yes
Scott, 1996[45]	Yes	Yes	Yes	Yes	Yes	No

NR, not reported.

Appendix 2. Quality Ratings for Studies on Antiviral Therapy (cont)				
Maintenance of Comparable Groups?	**Reporting of Attrition, Contamination, etc.?**	**Differential Loss to Follow-up or Overall High Loss to Follow-up?**	**Quality Rating**	**External Validity**
Yes	Yes	No	Good	International, multisite
Yes	Yes	No	Good	Multisite
Yes	Yes	No	Good	International, multisite
Yes	NR	NR	Fair	International, multisite
Yes	Yes	No	Good	Multisite
Yes	Yes	No	Good	Single research clinic site
Yes	Yes	No	Good	Recruited from community
Yes	NR	NR	Fair	Prenatal clinic, Texas
NR	NR	Yes	Poor	French maternity ward
No	Yes	NR	Poor	Prenatal clinic, Texas
NR	No	NR	Poor	England, 2 clinic sites
NR	Yes	NR	Poor	Texas hospital and clinic

Appendix 3. MEDLINE® Search Results



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