GENITAL HERPESVIRUS MANAGEMENT

Special Considerations for the Female Patient

Genital herpes simplex virus (HSV), a recurrent, incurable viral infection, is the most common ulcerative sexually transmitted disease (STD) in the United States.[1-3] Based on serum samples collected from individuals 12 years of age or older during the third National Health and Nutrition Examination Surveys (NHANES III, 1988 to 1994), the seroprevalence of HSV type-2 (HSV-2) with or without type-1 coinfection was 21.9%, or more than 1 of every 5 Americans.[4,5] This represents a 30% increase in HSV-2 seroprevalence from that measured by NHANES II (1976 to 1980).[4] Reflective of the gender difference in transmission susceptibility, NHANES III found a higher seroprevalence of HSV-2 among females, 25.6% compared to 17.8% among males.[3,4]

Based on these findings, as of 1994 there were an estimated 45 million HSV-2 infected individuals in the U.S., and an additional 1 million new cases are believed to occur each year.[4,6] More troubling is the fact that most HSV-infected individuals are unaware they are infected. Approximately 60% of all HSV-2 infections are undetected by patients and physicians due to an atypical clinical presentation, and another 20% have no visible clinical symptoms.[7]

The consequences of a HSV-2 infection are often significant. The pain and sequela of a primary episode can be severe and disabling, and the psychosocial morbidity of recurrent genital herpes can be life altering.[3,8,9] The risk of human immunodeficiency virus (HIV) transmission is increased with a HSV infection, with or without the presence of ulcerated lesions.[2,10] Furthermore, the morbidity and mortality of a HSV-2 infection is increased in immunocompromised individuals.[9] However, the most severely affected population is neonates infected during the birth process.[9] Maternal transmission of

HSV-2 to a neonate can result in developmental disabilities, permanent neurological damage, or death.[3,9]

HSV-2 infection, once considered a latent condition, is more likely to be a chronic, persistent infection.[7] The prevalence of subclinical activation and asymptomatic viral shedding is considerably greater than originally thought. Strategies to reduce transmission during subclinical shedding include abstinence, and the use of barrier contraception or chronic suppressive antiviral therapy.[1,3,11]

The educational objectives of this continuing medical education (CME) monograph are to:

- Be aware of the prevalence of HSV-2 infections in your female patients
- Know the capabilities of the diagnostic tools currently available
- Learn the recent advances in clinical management of genital herpes, including suppressive antiviral therapy
- Understand the risks of HSV-2 neonatal transmission
- Know the risk-prevention methods indicated for discordant couples
- Learn the appropriate psychosocial management of HSV-positive patients and their partners, based on the clinical course of HSV infections

The Transmission of HSV Infections

Not surprisingly, the risk of acquiring a HSV infection is a function of the extent of one's sexual exposure. Thus, the risk increases with age, time since the first sexual intercourse experience, and the number of lifetime sexual partners.[4,9]

As seen by the gender difference in seroprevalence reported in NHANES III,[4] the risk of HSV transmission is greater from an infected male to susceptible female, than

from infected female to male.[3] In a 1-year, prospective evaluation of heterosexual, discordant couples with untreated, unprotected, recurrent genital herpes, the overall incidence of genital herpes acquisition was 9.7%.[3] When analyzed by gender, however, the annual risk of acquiring genital herpes by a susceptible female partner was 18.9% and only 4.5% in a susceptible male partner.[3] This study also found that antibodies triggered by a HSV-1 infection seem to provide partial protection against infection with HSV-2.[3] The annual risk of HSV-2 acquisition by a susceptible partner without HSV-1 antibodies was 16%, but 7.2% in a susceptible partner with circulating HSV-1 antibodies.[3]

The most surprising finding in the study of genital herpes transmission in discordant couples was that 70% of HSV transmission occurred during times when the source partner was asymptomatic.[3] While the transmission of genital herpes is most likely to occur when the source partner has frequent and prolonged symptomatic episodes of clinical reactivation, the majority of genital herpes transmission in fact occurred due to asymptomatic viral shedding during subclinical reactivation.[3]

Numerous studies have found that the vast majority of HSV-2 seropositive individuals, from 66% to 91%, were unaware they were infected.[4,9] It is estimated that 60% of all HSV-2 infections have an atypical presentation, without genital lesions.[4,9] Only approximately 20% of all HSV-2 infections are truly asymptomatic, with subclinical episodes of viral shedding, or have reactivations in sites such as the cervix where lesions cannot be observed.[9]

In the female, HSV viral shedding can occur from the vulva, perineum, vaginal secretions, cervix, and urethral and perianal skin.[11,12] In the male, viral shedding can

occur from penile and urethral skin, sperm, and the perianal area.[11] To determine the incidence of subclinical shedding, a prospective study of 110 untreated female patients with confirmed, recurrent, symptomatic genital herpes compared their daily records of visible lesions with viral cultures of daily samples taken from their vulva, cervix, and rectum.[11] Subclinical shedding was found in 55% of the women infected with HSV-2, and 52% of the women infected with both HSV-1 and HSV-2.[11] In other studies, co-infection with HSV-1 increased the likelihood that HSV-2 reactivations would be subclinical and asymptomatic.[5] Half the episodes of subclinical shedding occurred within 7 days of a symptomatic recurrence.[11] Asymptomatic shedding was most common in women who had more than 12 symptomatic episodes per year, and those who had acquired genital herpes within 12 months of study enrollment.[11]

In a prospective study that examined the recurrence rate of clinical reactivation of genital herpes, a median of 4 symptomatic episodes occurred in the first year after acquiring a HSV-2 infection.[13] Only 11% of the 326 patients had no recurrent episode of genital herpes during the period of observation.[13] The frequency of recurrence was greater in males than females; the median monthly incidence of a genital herpes recurrence was 0.43 episodes for the male patients (n=101) and 0.33 episodes for the female patients (n=225) (*P*=.005).[13] The frequency of recurrence was also a function of the severity of the primary episode. When the duration of the primary episode was 35 days or longer, recurrent episodes were twice as frequent as when the primary episode was less severe or prolonged.[13]

The Diagnosis of HSV Infections

Accurate and definitive diagnosis of genital herpes is crucial for control of transmission and appropriate patient management. However, the clinical signs and symptoms of genital herpes can vary with the virulence of the infecting strain, the extent of an individual's immunologic competence, and the presence of circulating antibodies. Furthermore, the clinical presentation of genital herpes is often atypical or absent, so even highly trained specialists cannot rely on a patient's medical history or clinical appearance to detect genital herpes.[9]

A genital herpes infection is classified as either a primary episode, nonprimary first episode, or recurrent episode. In the past, genital herpes episodes were classified by clinical appearance, but it is now known that accurately identifying these episodes is impossible without virologic and serologic assays. An episode is considered a primary genital herpes infection if antibodies to both HSV-1 and HSV-2 are absent and the viral culture of a lesion specimen is positive for either HSV-1 or HSV-2. A nonprimary first episode of genital herpes occurs when the patient either acquires HSV-2 genital herpes confirmed by viral culture with preexisting HSV-1 antibodies confirmed by serologic assay, or acquires HSV-1 genital herpes with preexisting HSV-2 antibodies. Recurrent genital herpes is the reactivation of an existing infection, confirmed when the viral isolate recovered from the lesions or affected sites is the same HSV type as the circulating antibodies identified in the sera.[14]

The clinical presentation of a primary infection of genital herpes can range from an asymptomatic episode to an episode severe enough to require hospitalization.[3,14] The classic clinical course of a genital herpes infection is a painful or itchy prodrome,

followed by the development of bilateral genital lesions that evolve from vesicles to ulcers, eventually crusting and healing.[7,9,12] Systemic symptoms — tender inguinal lymphadenopathy, fever, headache, and malaise — when they occur, are often but not always restricted to the first episode.[14]

Although it had been thought that the signs and symptoms of genital herpes were more severe and prolonged during a primary HSV-2 episode than during a recurrent episode, this has been found to be a false assumption.[12,14] It is impossible to distinguish a primary episode from a recurrent episode by clinical appearance alone.[12] Genital lesions and local symptoms of pain and dysuria are common in both primary and recurrent episodes.[14] Furthermore, a primary or recurrent episode may have an atypical presentation, often mistaken for a yeast infection or allergic reaction, manifested as genital skin splits or fissures, furuncles, vaginal discharge, localized erythema or rash, anorectal irritation, or unexplained back pain.[7,9]

Given the unreliability of clinical identification, detection of HSV isolates by viral culture is the gold standard of genital herpes diagnosis. All undiagnosed genital lesions should be assayed for HSV virus.[9] However, the reliability of viral isolation in tissue culture depends on proper specimen collection and transport to a diagnostic virology laboratory. Active lesions should be scraped or vesicle fluid aspirated to harvest live viral isolates.[15] Equally important is the proper transport of the specimen, usually in virus transport media (unless polymerase chain reaction [PCR] is going to be employed) and on a cold pack that will not freeze the sample.[15] The ability of a genital lesion sample to infect cells in tissue culture declines when the viral expression declines, as seen during recurrent or subclinical episodes.[9] While a viable diagnostic tool, this

method is only useful when live viral isolates can be harvested from an active herpes virus lesion.

The detection of circulating HSV-1 or HSV-2 antibodies is a useful adjunct to detecting viral isolates from an active lesion site.[15] In fact, a type-specific serologic assay is the only way to detect subclinical genital herpes infections.[15] Structural proteins of the HSV virion, especially the viral envelope glycoproteins, provoke HSV antibody production.[7] For the most part, these glycoproteins have antibody binding sites, or epitopes, that are functionally identical for HSV-1 and HSV-2, or type-common.[7] Two viral envelope glycoproteins elicit type-specific antibodies — glycoprotein G-1 (gG-1) and gG-2, and glycoprotein C-1 (gC-1).[7,9]

Until very recently, the only serologic tests commercially available were type-common assays that may have falsely claimed to discriminate between HSV-1 and HSV-2 antibodies.[16] These non-specific assays are of no value in detecting HSV-2 seroconversion in individuals who are already seropositive for HSV-1.[7] According to NHANES III, the seroprevalence of HSV-1 without HSV-2 coinfection is 51% of all individuals 12 years old or older.[5]

For over 15 years, research and academic laboratories have relied on gG-based type-specific Western blot and immunodot enzyme assays to differentiate between HSV-1 and HSV-2 antibodies.[15] While highly accurate, these assays cannot be batched, and require several days and a high level of skill to perform and interpret.[7,9,15-17]

The Food and Drug Administration (FDA) has recently approved 4 commercially available gG-based type-specific serologic assays for HSV-1 or HSV-2. Focus Technologies provides 3 gG-based assay kits for adult and pregnant patients, a HSV-1

and a HSV-2 enzyme-linked immunosorbent assay (ELISA), HerpeSelect™ ELISA 1 and HerpeSelect™ ELISA 2, and an immunoblot test combining HSV-1 and HSV-2 antibody detection.[16] The Diagnology test is POCkit® HSV-2, the only point-of-care test for HSV-2 antibodies for use in the clinic for adult patients.[16]

The HerpeSelect™ ELISA assays can be performed on batched specimens using an automated platform; the immunoblot assay, suited for individual specimens, resembles the Western blot assay with gG-1 and gG-2 bands and a control band on a single colorimetric strip that can be read visually.[16] The POCkit® HSV-2 assay, which uses capillary blood from a finger stick, can be performed without laboratory equipment in minutes.[16]

Both the FDA and the Centers for Disease Control and Prevention (CDC) used the Western blot assay as a reference standard for evaluating the sensitivity and specificity of these assays. The ELISA assays have a sensitivity of 96%-100%; the immunoblot, 93%-100%; and the POCkit assay, 93%-100%.[16,18,19]

Another measure of sensitivity is the amount of time after HSV acquisition before the test can detect seroconversion. This is determined in part by the typical time required to mount an antibody response to a particular protein and in part by whether the assay can detect the earlier immunoglobulin (Ig) M as well as the later IgG response.[9,20] The viral protein gG tends to elicit an antibody response relatively late, from 2 to 6 months after exposure.[9] Studies of the time to detection with the new gG-based assays are limited, but HSV-2 seroconversion after a primary or nonprimary first episode can be detected within a median of 2 weeks of the onset of symptoms with the POCkit® HSV-2 assay, which may detect IgM responses to gG-2.[16,17,20]

Seroconversion following HSV-1 exposure may take longer, and assays for HSV-1 antibodies tend to be slightly less sensitive than for HSV-2 antibodies.[16] However, approximately 5% of the population never develop antibodies to HSV-2 gG.[15] Of course, no assay of HSV antibodies can differentiate between an oral and genital infection.[16]

The Treatment of HSV Infections

Once a HSV infection is acquired, no available chemotherapeutic agent can eradicate the virus.[1] However, there are three orally administered antiviral agents currently available in the US to manage genital herpes infections. Acyclovir, the standard treatment for genital herpes for nearly two decades, is a purine nucleoside analog that suppresses HSV activity by inhibiting HSV DNA polymerase, blocking HSV DNA chain elongation and termination.[1,21] Valacyclovir, a valine ester prodrug of acyclovir, has greater bioavailability than acyclovir due to enhanced intestinal absorption.[1,18] Famciclovir, a prodrug of penciclovir, is also a purine nucleoside analog that inhibits HSV DNA polymerase, disrupting chain replication.[1] Like valacyclovir, famciclovir has higher oral bioavailability than acyclovir.[1] All three agents rely on the activity of the HSV viral enzyme thymidine kinase for conversion to their therapeutically active form, which is present only when the HSV is non-quiescent.[1] Randomized, placebo-controlled clinical trials have shown that treatment with any of the antiviral medications can significantly reduce the severity and duration of a first or recurrent episode, and daily therapy can reduce the frequency of recurrent episodes by 70%-80% among patients who have frequent recurrences (≥6 episodes/year).[1,18,22]

Because the severity of a primary genital herpes infection can be progressive, most patients should receive antiviral treatment regardless of the initial clinical

manifestations.[18] The recommended regimens for primary genital herpes are acyclovir 400 mg tid or 200 mg 5 times/d, valacyclovir 1,000 mg bid, or famciclovir 250 mg tid. The antiviral agent should be taken for 7 to 10 days or until the lesions have healed.[18] In several randomized comparative trials, the safety and efficacy of valacyclovir 1,000 mg bid or famciclovir 250 mg tid was not significantly different than acyclovir 200 mg 5 times/d in 10-day treatment of a first episode of genital herpes.[1]

Recurrent genital herpes can be managed with either episodic or chronic suppressive antiviral therapy. When the annual incidence of genital herpes recurrences is not troubling, a patient may elect to treat the infection episodically. The time to cessation of symptoms, viral shedding and complete healing can be shortened significantly when the patient initiates antiviral therapy at the onset of the first clinical symptom or prodrome.[1,23,24]

The recommended regimens for episodic antiviral therapy are acyclovir 400 mg tid or 200 mg 5 times/d for 5 days, famciclovir 125 mg bid for 5 days, or valacyclovir 500 mg bid for 3 days or until signs and symptoms of the outbreak are resolved.[1,7,18,23,24] Valacyclovir 500 mg bid or famciclovir 125 mg bid was comparable to acyclovir 200 mg 5 times/d in patient-initiated, 5-day treatment of recurrent genital herpes.[1,25] In patients who can be managed with a 3-day course of valacyclovir, the regimen is a 40% reduction from the standard 5-day course of episodic antiviral therapy, with the benefit of a 40% reduction in drug exposure and cost of therapy.[7]

Chronic suppressive antiviral therapy is another way to manage frequent outbreaks of genital herpes. Decreasing the frequency and severity of genital herpes outbreaks can be a significant benefit to the patient, relieving the psychosocial impact of having an

incurable sexually transmitted disease. In addition, chronic suppressive therapy (CST) may reduce subclinical shedding and the risk of transmitting the virus. A small, placebo-controlled trial of a 70-day course of suppressive therapy with acyclovir 400 mg bid was found to significantly reduce, but not completely eliminate, subclinical shedding in women with recently acquired HSV-2.[26]

Since acyclovir was first introduced, several sequential trials have documented the long-term safety and efficacy of CST with acyclovir. A large population with a prior history of frequent genital herpes outbreaks, treated with daily acyclovir 400 mg bid, have been followed now for over 15 years.[21,27-29] In these reports, the mean number of outbreaks was reduced with CST by more than 80%, and the severity and duration of episodes was attenuated when they did occur.[21,27,29]

Furthermore, the annual outbreaks have remained significantly suppressed over time with CST.[21] A study that examined the effect of CST with acyclovir on the clinical course of the disease found that after 6 years of CST, 75% of the study cohort switched to episodic treatment for the 7th year experienced at least 2 recurrent outbreaks.[27] In these studies, adverse events were minor, mostly headache or nausea, which tended to remit with time. Based on the safety profile of acyclovir, no clinical laboratory monitoring is required.

In 2 dose-ranging studies of CST with famciclovir, one for 4 months and the other for 12 months, a regimen of 125 mg or 250 mg tid or 250 mg bid was safe and effective in suppressing a recurrence of genital herpes.[30,31] During the first 6 months of CST with one of these 3 regimens of famciclovir, the percentage of patients who experienced no HSV recurrence was 79% to 86%.[31]

Similar efficacy was seen with valacyclovir, the only anti-herpes therapy with a once-daily regimen.[28] Eighty percent of the patients receiving valacyclovir 500 mg qd for 1 year experienced only one or no outbreaks.[28] However, valacyclovir 1,000 mg qd appears to be more effective in patients who have very frequent (>9 episodes/year) recurrences.[18] The high level of suppression achieved with valacyclovir may be attributed to the higher oral bioavailability and greater compliance with the once-daily regimen of valacyclovir compared to CST with acyclovir.[28] Adverse events with valacyclovir were similar to those reported for the placebo cohort.[28] The results of a landmark longitudinal study measuring the impact of CST with valacyclovir on HSV transmission among discordant couples will be presented at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy in September of this year.

The recommended regimens for CST are acyclovir 400 mg bid, famciclovir 250 mg bid, or valacyclovir 500 mg qd for patients with ≤9 recurrent episodes per year and 1,000 mg qd for patients with >9 recurrent episodes per year.[18,32] Acyclovir is the least expensive of the three antiviral agents,[22] but the less frequent dosing requirement of valacyclovir regimens has been shown to increase compliance, an important consideration with chronic therapy.[28] Although two studies have found approximately 3% of isolates recovered from recipients of CST have demonstrated acyclovir resistance, CST has not been associated with the emergence of clinically significant resistance among immunocompetent patients.[26]

In addition to providing anti-herpes therapy, patient counseling is an important aspect of managing patients who have genital herpes. The clinical course of the disease should be explained, with emphasis on the potential for recurrent episodes,

asymptomatic viral shedding, and sexual transmission. Patients should be advised to abstain from sexual activity when lesions or prodromal symptoms are present and encouraged to inform their sex partners that they have genital herpes. The use of condoms during all sexual exposures with new or uninfected sex partners should be encouraged. Although initial counseling can be provided at the first visit, many patients benefit from learning about the chronic aspects of the disease after the acute illness subsides.

Maternal and Neonatal Acquisition of a HSV Infection

The clinical consequences to the fetus of maternal HSV acquisition during pregnancy are significant. Maternal acquisition of a primary HSV infection is associated with a three-fold increase in the risk of spontaneous abortion, and acquisition during the second or third trimester of pregnancy can result in premature birth.[14,33] If hematogenous transmission of HSV to the fetus occurs in utero during the 12th to 14th week of pregnancy, severe neurologic defects can develop.[14] But the most significant consequence of maternal HSV infection is perinatal transmission, which can cause substantial neonatal morbidity and mortality despite postpartum antiviral treatment.[34,35]

Maternal transmission of HSV to the neonate can occur when the fetus is exposed to viral particles during passage through the birth canal.[14] The risk of neonatal HSV transmission is greatest when the mother acquires a primary HSV-1 or HSV-2 infection close to the time of labor, about 50% when the infection is primary and 30% when the infection is a nonprimary first episode.[9,14,15,18,35] Due to the time necessary to develop HSV antibodies, maternal circulating antibodies are not present within the first several months of a primary HSV infection and thus immunologic protection cannot be passed

to the fetus in utero.[12,14,33,36] The risk of neonatal transmission is much less, between 1% to 5%, when the mother acquired genital herpes during the first half of pregnancy or earlier, and experiences a recurrent activation at the time of delivery.[9,14,15,18,35]

In order to prevent neonatal transmission of HSV, cesarean delivery is employed whenever a mother has a clinically evident HSV episode at the onset of labor. Delivery by cesarean section, a highly invasive procedure, is associated with risks to both the mother and the neonate. Furthermore, abdominal delivery does not completely eliminate the risk of HSV transmission to the neonate.[18] A better strategy to prevent neonatal acquisition of HSV is to prevent maternal acquisition of genital herpes during late pregnancy by susceptible women, and to prevent clinical or subclinical reactivation of HSV at the time of delivery by women already infected.

The overall odds of a pregnant woman acquiring genital herpes during her pregnancy have been estimated at about 1% to 5%.[14,15,33,36] However, when the mother is seronegative for HSV-1 or HSV-2 and her partner is HSV-2 seropositive, the risk of transmission is as high as 30%.[15] In 1992, a survey of susceptibility found that 9.5% of pregnant women were at risk of acquiring HSV-2 genital herpes during her pregnancy from her infected partner.[36]

To identify these women at risk, type-specific serologic assays should be performed on all expectant mothers and their partners early in the pregnancy. Furthermore, the HSV status of women at risk of acquiring genital herpes should be routinely monitored by type-specific serologic assays from the onset of the third trimester of the pregnancy.[18,35] Susceptible women whose sexual partners have an oral or genital HSV infection, or whose partners' infection status is unknown, should be counseled to avoid

unprotected genital and oral sexual contact during the last trimester. HSV-infected male partners should be encouraged to use chronic suppressive antiviral therapy, at least during the last stage of their partner's pregnancy.

Women with recurrent genital herpes also should be identified by type-specific serology. A genital herpes episode is often asymptomatic or has an atypical presentation, so reliable diagnosis of a primary or recurrent genital infection cannot be made by physical examination.[12] Furthermore, a woman's cellular immunity declines during a pregnancy, so it is possible for a long-standing asymptomatic HSV infection to become clinically evident for the first time in the third trimester of gestation.[37] Most infants who acquired a perinatal HSV infection were born of mothers who had no history of clinically evident genital herpes.

Pregnant women with primary or recurrent genital herpes may be managed with suppressive antiviral treatment in late pregnancy, to reduce viral shedding and the likelihood of recurrent episodes.[14,18] The safety of anti-herpes therapy in pregnant women has not been established in large clinical trials; acyclovir has a FDA pregnancy category C status and famciclovir and valacyclovir have a category B status.[14,38] However, in 1984 the manufacturer of acyclovir, in collaboration with the CDC, established a registry to track the clinical outcome of acyclovir use in pregnancy.[38] As of 1993, in 311 infants exposed to acyclovir in utero, there was no evidence of an increased risk for birth defects.[38]

The outcome from several preliminary trials suggests acyclovir treatment in late stage pregnancy reduces the incidence of recurrent episodes at term and thus reduces the need for cesarean delivery to protect the neonate.[18,39,40] A trial of acyclovir in

women who experienced their first clinically evident genital herpes episode during their pregnancy were randomized to treatment with acyclovir 400 mg tid (n=21) or placebo (n=25) from the 36th week of their pregnancy to term.[39] Suppressive therapy with acyclovir significantly reduced the incidence of recurrent episodes detected by viral culture at delivery, as well as the number of deliveries by cesarean section.[39] In the acyclovir cohort, there were no incidences of subclinical viral shedding, recurrent genital herpes, or cesarean section delivery, and 9/25 (36%) cesarean deliveries due to recurrent genital herpes in the placebo cohort (*P*=.002).[39] No adverse events were observed in the neonate during the first month postpartum.[39]

In a second trial, pregnant women with recurrent genital herpes were randomized to treatment with acyclovir 200 mg qid (n=31) or placebo (n=32) from week 36 to term.[40] There was a significant decrease in clinical recurrences documented by viral cultures, and a nonsignificant decrease in cesarean deliveries among the women treated with acyclovir.[40] Based on pharmacokinetic studies of acyclovir in pregnant women, it is likely that plasma levels of acyclovir dropped below therapeutic levels with the 200-mg qid dose.[41]

The pharmacokinetics of acyclovir or valacyclovir in the last weeks of pregnancy have been found to be similar to their pharmacokinetics in non-pregnant adults, despite the extensive maternal physiologic changes that occur during late pregnancy.[34,41] In one pharmacokinetic study of acyclovir administered to pregnant women with recurrent genital herpes, 7 women received acyclovir 200 mg tid and 8 received acyclovir 400 mg tid, from week 38 to term.[41] Based on steady-state peak and trough levels, the 400-mg tid dose was found to be necessary to maintain therapeutic levels in the serum of

pregnant women.[41] Acyclovir was concentrated in amniotic fluid but there was no accumulation of acyclovir in fetal blood. This short course of suppressive acyclovir was well tolerated, with no evidence of toxicity to the mother or neonate.[41]

A second, phase I pharmacokinetic study of suppressive anti-herpes treatment of recurrent HSV infection in late-stage pregnancy examined both acyclovir and valacyclovir.[34] Ten women were randomized to treatment with acyclovir 400 mg tid and 10 to treatment with valacyclovir 500 mg bid, from week 36 to term.[34] Significantly higher mean plasma levels of acyclovir were achieved with valacyclovir than with acyclovir (P<.001).[34] However, none of the study participants in either cohort experienced genital HSV recurrence or asymptomatic viral shedding at the time of delivery.[34] Acyclovir was concentrated in the amniotic fluid but not in fetal blood in both cohorts. Both acyclovir and valacyclovir were well tolerated and there was no evidence of drug toxicity.[34]

Based on the findings of these small trials, the American College of Obstetricians and Gynecologists issued clinical management guidelines that endorse consideration of antiviral treatment for pregnant women experiencing a primary genital herpes episode, especially at or beyond the 36th week of gestation.[14] Furthermore, according to consensus and expert opinion, antiviral viral therapy at or beyond the 36th week of gestation may be considered for pregnant women who are at risk of recurrent genital herpes.[14]

The recommended antiviral dosages for suppression in late pregnancy are acyclovir 400 mg tid, valacyclovir 500 mg bid, or famciclovir 250 mg bid.

Diagnosing Gestational Herpes

Precise classification of a HSV infection is critical, especially during a pregnancy, when misclassification of gestational genital herpes can result in unnecessary exposure of the fetus to extended antiviral treatment, needless delivery by cesarean section, or inappropriate counseling of the parents.[37] However, correct classification of a HSV infection can only be accomplished when clinical evaluation is accompanied by viral culture and type-specific serology.[12]

Due to the absence of readily accessible type-specific HSV-2 serologic assays in the past, misdiagnosis of gestational herpes was undoubtedly widespread.[42] In a 45-month inception cohort study, the prevalence of gestational genital herpes among women with no history of a HSV infection was surprisingly common.[42] HSV-2 antibodies were detected by Western blot assay in 439 of 1,355 pregnant women (32%) participating in the study.[42] Similar results were found in a smaller study of 277 pregnant patients in private obstetrical practices.[35] The seroprevalence of HSV-2 among the study participants was 32%; two thirds of the seropositive women had no history of genital herpes.[35]

A few years ago a 33-month survey of women receiving prenatal care in one of four medical centers was conducted to evaluate the accuracy of gestational genital herpes diagnoses based on clinical signs and symptoms.[12] Out of approximately 26,037 pregnant women, 23 were initially diagnosed with primary genital herpes due to the severity of the clinical presentation.[12] When gG-based HSV-2 enzyme immunoassays were preformed, only 1 HSV-2 infection was a primary episode of genital herpes.[12] The

serologic results revealed 19 (83%) were actually experiencing a recurrent HSV-2 infection and 3 (13%) were reclassified as a nonprimary first episode of genital herpes.[12]

The misleading physical presentation of gestational HSV infection can be seen in two representative case histories. In the first case, the patient presented at the 30th week of her gestation complaining of flu-like systemic signs and symptoms, and numerous painful lesions on both the labia and perineum.[37] A viral culture and PCR assay for HSV DNA revealed the presence of HSV-2. However, despite the severity of the clinical appearance, HSV serology by Western blotting detected both HSV-1 and HSV-2 antibodies, confirming a diagnosis of recurrent genital herpes.[37]

The second patient, on the other hand, complained only of a painful area on her genitalia without any systemic signs or symptoms, during a routine prenatal visit in the 34th week of her second pregnancy.[37] Upon examination, a single tender, perineal ulceration was seen.[37] The presence of HSV-2 isolates was confirmed by viral culture and PCR assay for HSV DNA, but the patient was seronegative for either HSV-1 or HSV-2 antibodies.[37] Despite the mild clinical appearance, this patient was experiencing a primary genital herpes infection.[37]

Conclusion

Herpes simplex virus is a prevalent condition, especially among female patients. Most transmission of HSV is due to a lack of awareness of infectivity during periods of subclinical viral shedding. Because most genital herpes infections are atypical or asymptomatic, diagnosis by physical examination is unreliable. Type-specific diagnosis with serologic assays is now possible and should be routinely employed, especially with obstetric patients. Safe and effective antiviral therapy can be taken to attenuate

infrequent HSV episodes when they occur, or chronically to suppress frequent recurrences and subclinical shedding. The risks of neonatal transmission can be reduced significantly with routine screening and counseling of both the obstetrical patient and her partner, and late pregnancy treatment with an anti-herpes agent where indicated.

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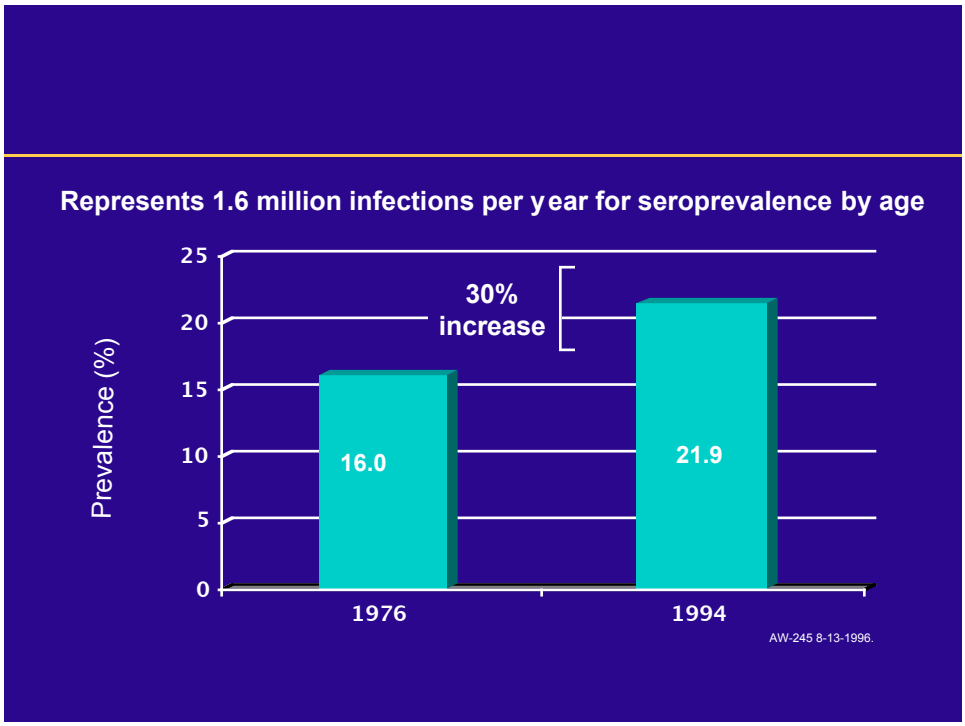
Graphics

Figure 1. Increase in HSV-2 Seroprevalence from 1976 to 1994[4]



Surveyed individuals 12 years of age or older.

Figure 2. The Clinical Spectrum of HSV-2[9]

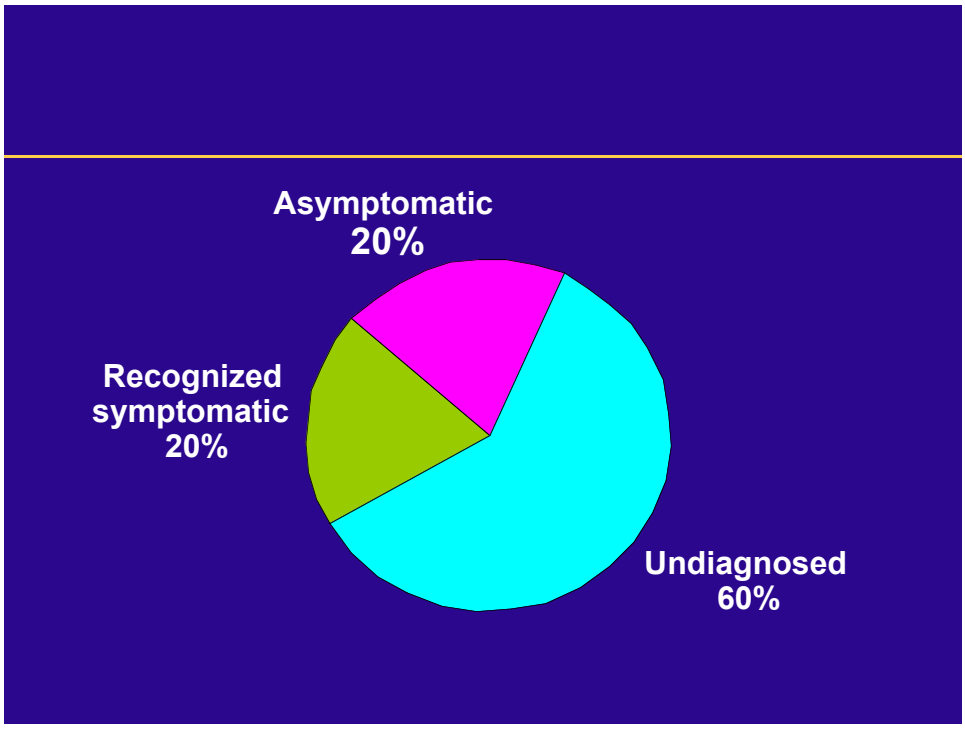


Figure 3. Prevalence of Unrecognized HV-2 Infections[4]

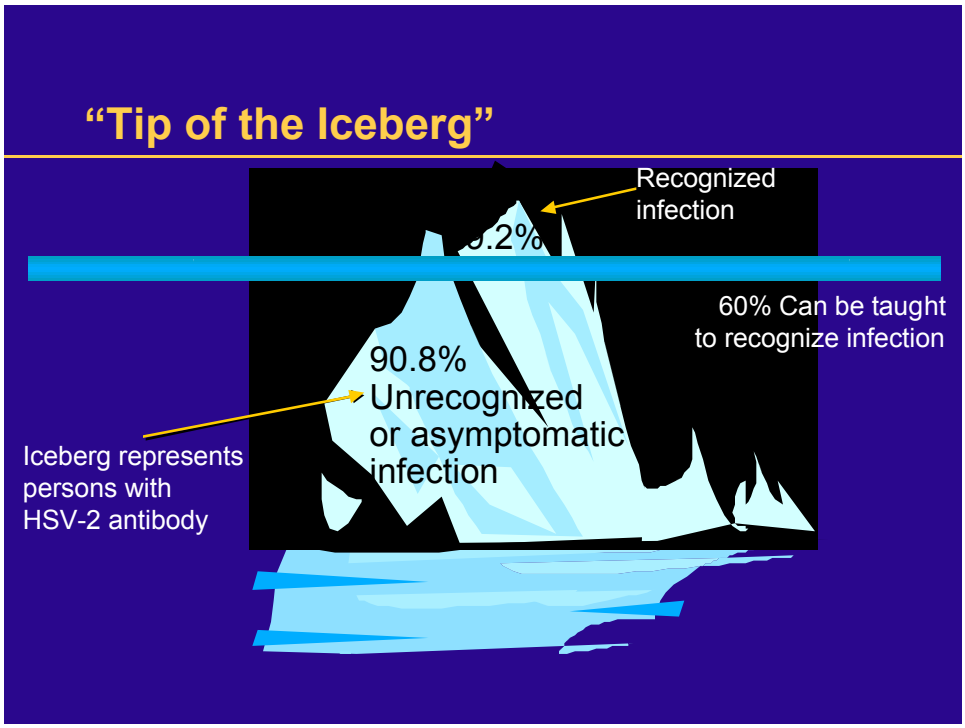


Figure 4. Incidence of HSV-2 Recurrence in First Year[13]

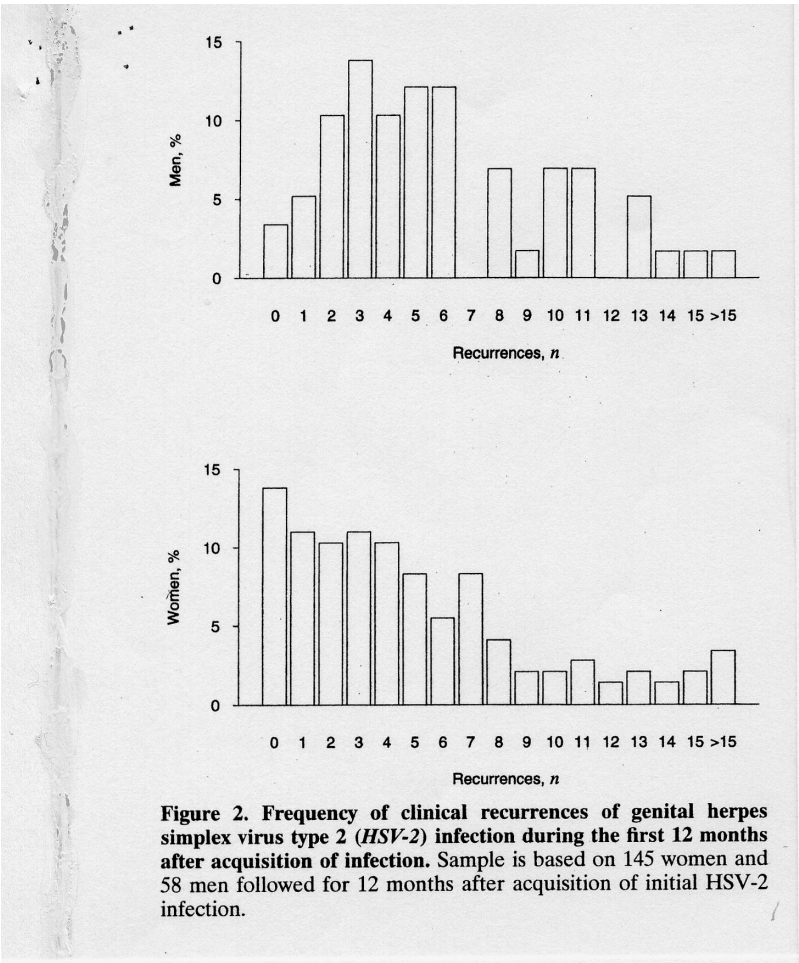


Figure 2. Frequency of clinical recurrences of genital herpes simplex virus type 2 (*HSV-2*) infection during the first 12 months after acquisition of infection. Sample is based on 145 women and 58 men followed for 12 months after acquisition of initial HSV-2 infection.

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Figure 5. Determination of Genital Herpes Episode Classification[37]

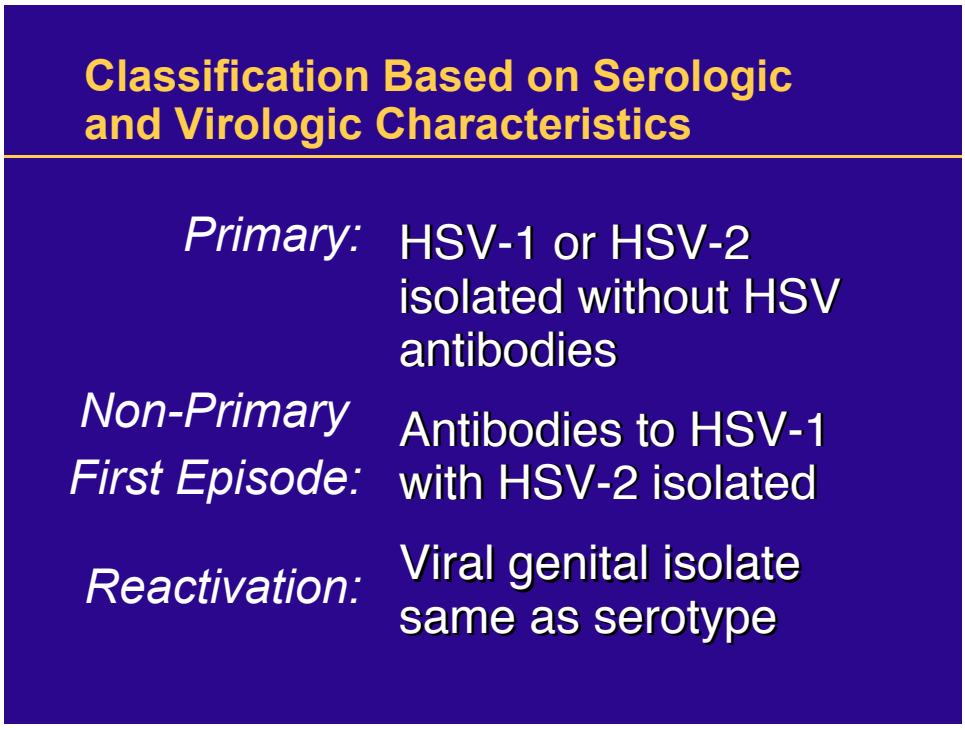


Figure 6. HSV Viral Proteins[17]

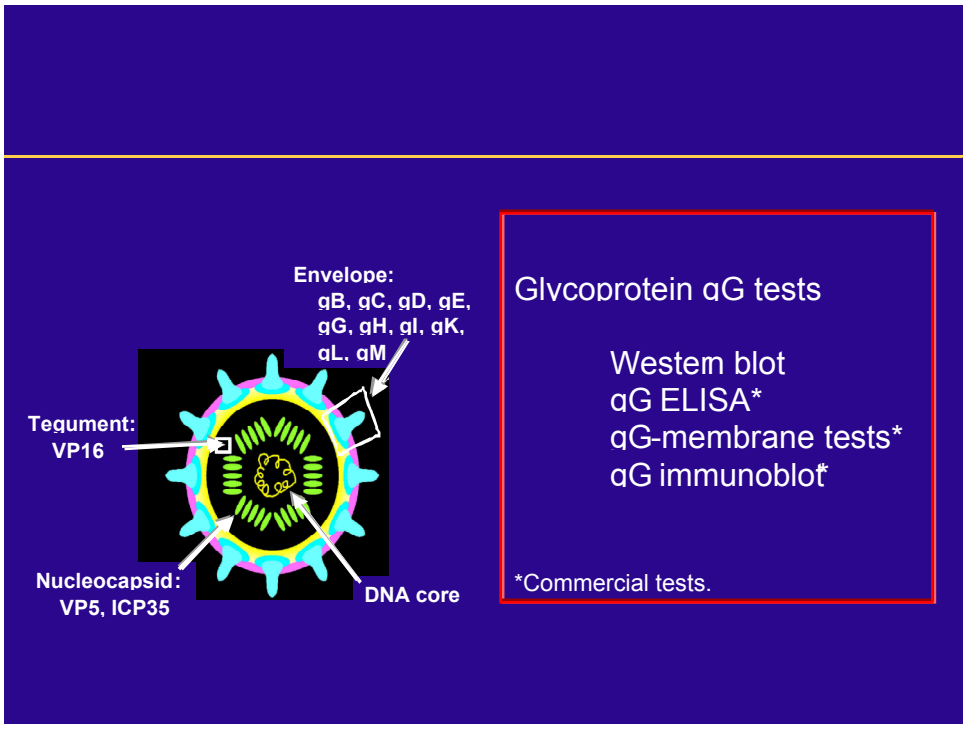
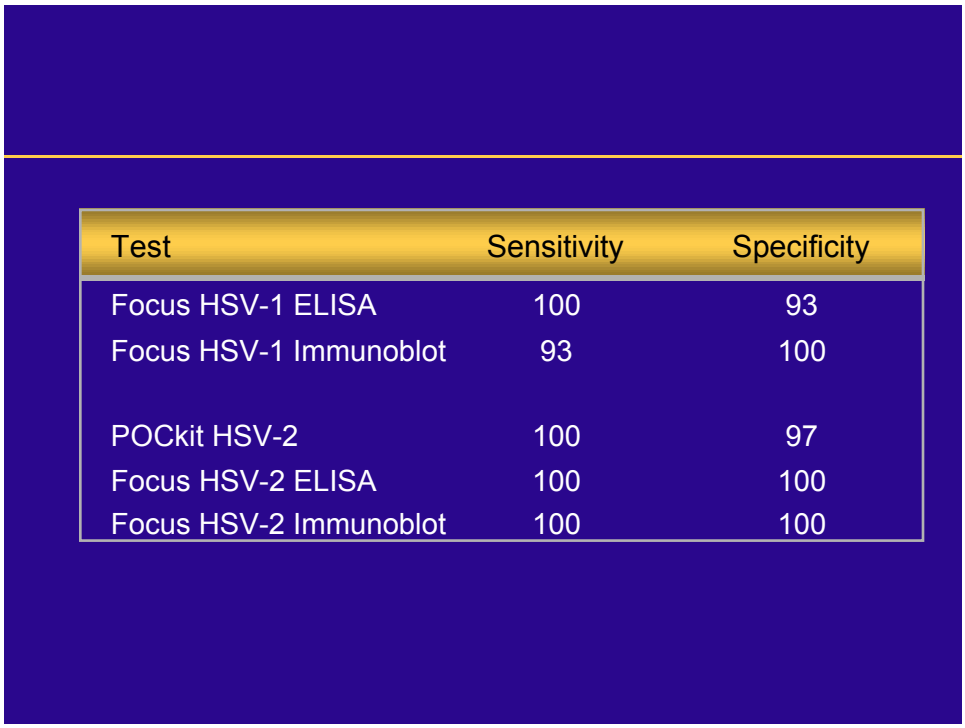


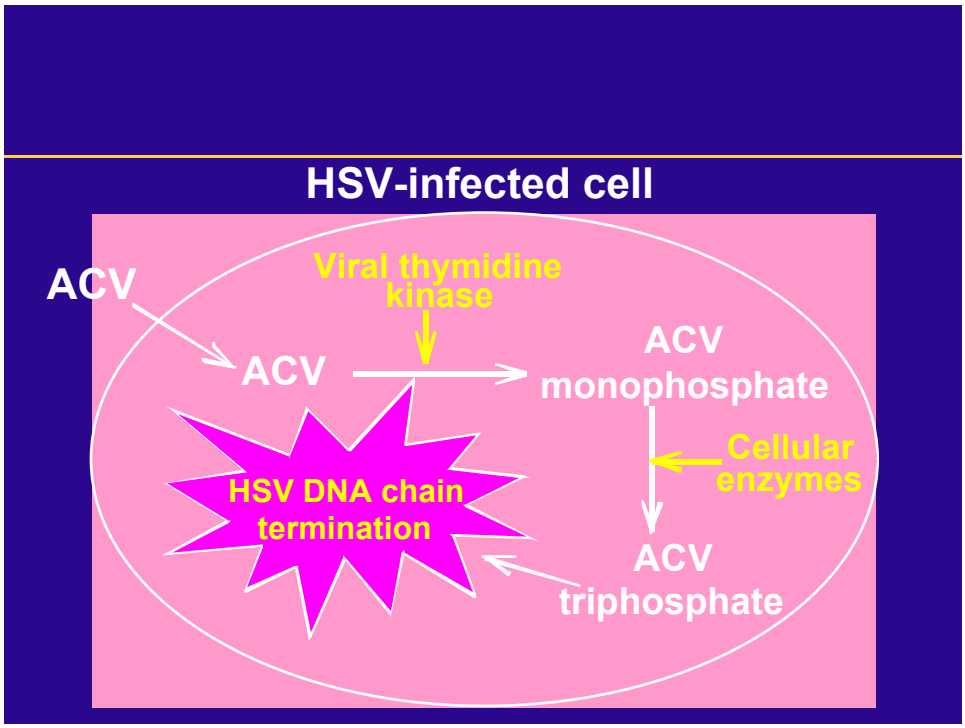
Figure 7. CDC Evaluation of gG-based Commercial Assays[19]



Test	Sensitivity	Specificity
Focus HSV-1 ELISA	100	93
Focus HSV-1 Immunoblot	93	100
POCkit HSV-2	100	97
Focus HSV-2 ELISA	100	100
Focus HSV-2 Immunoblot	100	100

CDC panel results are presented as a means to convey further information on the performance of these assays with a masked, characterized serum panel. This does not imply an endorsement of the assays by the CDC.

Figure 8. Mechanism of Action of Acyclovir



ACV = acyclovir

Figure 9. Clinical Equivalence of 3- and 5-Day Treatment with Valacyclovir[8]

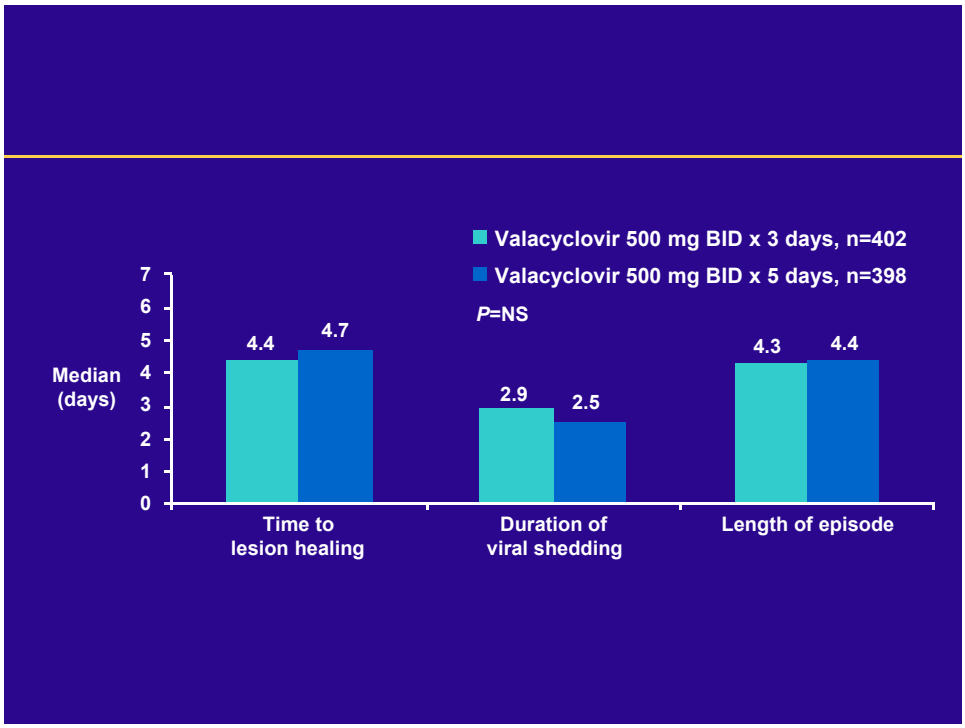
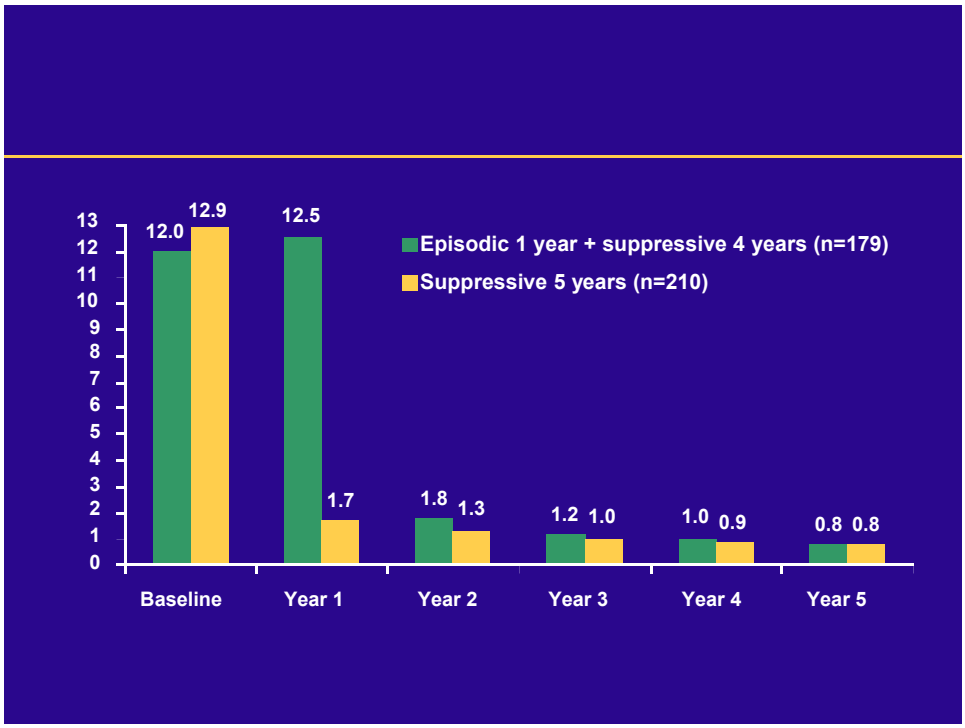


Figure 10. Recurrence Significantly Suppressed Over Time with Acyclovir CST[21]



CST = chronic suppressive therapy

Figure 11. First Symptomatic Reactivation of Genital Herpes in Week 30 of Pregnancy

[please insert slide #11 from the Brown presentation]

This patient presented with clinical signs and symptoms typically seen with a primary genital herpes episode. However, viral culture and HSV DNA by PCR were positive for HSV-2, and a type-specific Western blot assay was positive for antibodies to both HSV-1 and HSV-2, indicating a reactivation of an existing genital herpes infection.[37]

Figure 12. Atypical Primary Genital Herpes in Week 34 of Pregnancy

[please insert slide #7 from the Brown presentation]

Clinical examination revealed a single, tender perineal ulceration stained with Toluidine blue prior to photography. While viral culture and PCR analysis for HSV DNA were

positive for HSV-2, a type-specific Western blot assay revealed no antibodies to HSV-1 or HSV-2 in the maternal sera, indicating a primary episode of genital herpes.[37]

CME Questions

1. The seroprevalence of herpes simplex virus type-2 (HSV-2)

   a correlates with the clinical prevalence of HSV.

   b is greater in males than in females.

   c has increased 30% since 1976.

   d is nearly 1 in every 3 adult Americans today.

Answer: c

2. The transmission of a HSV-2 infection

   a occurs more easily from a male partner to a susceptible female partner.

   b usually occurs during an asymptomatic episode of viral shedding.

   c can occur during neonatal passage through the birth canal.

   d All of the above.

Answer: d

3. Reliable diagnosis of an ongoing primary HSV-2 episode

   a. can be made by its clinical signs and symptoms.

   b. can be made with a type-specific serologic assay.

   c. can be made with a virologic assay.

   d. None of the above.

Answer: d

4. Type-specific serologic assays

a. can discriminate between oral herpes and genital herpes.

b. can discriminate between a primary episode and a recurrent episode.

c. can discriminate between a HSV-1 infection and a HSV-2 infection.

d. can diagnose a patient who has just been exposed to HSV.

Answer: c

5. Episodic treatment of genital herpes

a. is indicated when outbreaks are infrequent and not troublesome to the patient.

b. should be patient-initiated.

c. can be effective with a 3-day course of valacyclovir therapy.

d. All of the above.

Answer: d

6. Chronic suppressive antiviral therapy with valacyclovir

a. can be taken once daily.

b. can alter the course of a genital herpes infection.

c. requires frequent clinical laboratory monitoring.

d. has been available for nearly 2 decades.

Answer: a

7. Clinical strategies to prevent neonatal transmission of HSV call for

a type-specific serologic assays to identify women at risk of acquiring a primary genital herpes infection during their pregnancy.

b type-specific serologic assays to identify sexual partners of pregnant women capable of transmitting genital herpes.

c counseling discordant couples to avoid oral or unprotected sexual contact during the last trimester.

d All of the above.

Answer: d

8. The treatment of genital herpes in pregnancy calls for

a. chronic suppressive antiviral therapy during the last trimester for women with recurrent genital herpes.

b. episodic antiviral treatment of outbreaks from gestation week 36 to term.

c. chronic suppressive antiviral treatment of a primary episode from gestation week 36 to term.

d. All of the above.

Answer: c