Herpes Simplex Virus

Updated: June 27, 2018
Reviewed: June 27, 2018

Panel's Recommendations
I. Will condoms (compared with not using condoms) prevent herpes simplex virus (HSV) infection in sexually active adolescents and young adults with HIV? • Condoms should be used to prevent HSV infection (and other sexually transmitted diseases) in adolescents and young adults with HIV (strong; low). The data regarding the level of protection provided by condoms are very limited for individuals with HIV in general, and for youth specifically.
II. Will adolescents and young adults with HIV who have recurrent, genital HSV infection benefit from suppressive anti-HSV antiviral therapy (compared with not using suppressive therapy)? • Adolescents and young adults with HIV who suffer severe, frequent, and/or troubling recurrent genital HSV infection will benefit from anti-HSV suppression therapy (strong; moderate).
III. Should children and adolescents with HIV who have severe primary or recurrent HSV (genital or orolabial) infection receive intravenous (IV) acyclovir (compared with receiving oral antiviral therapy)? • Children and youth with HIV who have severe mucocutaneous HSV infections should be treated with IV acyclovir. When improvement is noted, they can be switched to oral therapy until healing is complete (strong; moderate).
IV. Should children and adolescents with HIV be treated with oral acyclovir, valacyclovir, or famciclovir for non-severe primary episodes or recurrent episodes of orolabial or genital HSV (compared with no antiviral therapy)? • Oral anti-HSV drugs will shorten the duration and reduce the severity of non-severe HSV infections in children and adolescents with HIV. Oral valacyclovir and famciclovir have superior pharmacokinetic profiles compared with oral acyclovir (strong; moderate).
V. Is foscarnet the best choice for anti-HSV therapy for children and adolescents with HIV in whom therapy is failing because of acyclovir-resistant HSV? • Foscarnet is the therapy of choice for acyclovir-resistant HSV (strong, very low). Ideally, the viral isolate should be tested to determine the antiviral resistance pattern.
Rating System *Strength of Recommendation: Strong; Weak* *Quality of Evidence: High; Moderate; Low; or Very Low*

Epidemiology

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) can cause disease at any age. It is generally regarded that HSV-1 is transmitted primarily through contact with infected oral secretions and that HSV-2 is acquired primarily through contact with infected genital secretions. However, among some populations of older adolescents and young adults, HSV-1 is the cause of a large proportion of first episodes of genital HSV infection.[1-4] In the United States, HSV-1 seroprevalence reaches 30% by adolescence.[5-7] Seroprevalence is higher among children who live below the poverty level and in non-Hispanic black children and children born in Mexico or of Mexican heritage.[5,6] The seroprevalence of HSV-1 approaches 60% in older adults. HSV-2 seroprevalence before reported onset of sexual activity is low (approximately 2%); rises to 20% to 26% in adults 30 to 49 years, and is higher in

non-Hispanic blacks, individuals with multiple sex partners and early age of onset of sexual activity, females, and in those living below the poverty level.[6,7] Among young adolescent girls, a longer history of sexual activity and another sexually transmitted disease in the past 6 months was associated with HSV-2 seropositivity.[8] These epidemiologic data indicate that children are at significant risk for primary infection or reactivation with HSV-1 and/or HSV-2 throughout childhood and adolescence. The age-specific seroprevalence of both HSV types is higher in many developing countries.[9-11]

Young children generally acquire HSV-1 from the oral secretions of caretakers or playmates. Rarely is this the result of contact with active herpetic lesions; infection most often results from exposure to HSV shed asymptomatically in the saliva of the contact. Salivary shedding of HSV detected by polymerase chain reaction (PCR) in adults who are HSV-1-seropositive is frequent (9% to 30% of days).[12-14] Older individuals who avoided infection during childhood or adolescence also acquire HSV-1 (oral or genital) from exposure to infected saliva. HSV-2 is more likely to be acquired during adulthood or adolescence than in childhood as it is typically sexually transmitted. Genital shedding of HSV-2 by women who do not have HIV, as detected by PCR, is frequent (19% of days).[12] Either HSV type can be transmitted by oral-oral, oral-genital, and genital-genital contact. In general, shedding of oral HSV persists longer in young children. Oral and genital HSV shedding is more common in close proximity to the first episode of infection and in patients with HIV (30% of days in individuals who are HSV seropositive and not on antiretroviral therapy [ART]).[15,16]

HSV infection can be acquired as a neonatal infection, primarily through exposure to HSV-infected maternal fluids during vaginal delivery; less commonly, infection may occur *in utero*.[17,18] Newborns are infected infrequently from oral secretions of an adult caretaker. The risk of transmitting HSV during delivery is approximately 1% in pregnant women with remote primary HSV infection, whereas the risk is much higher for infants born to women with recent HSV infection (range: 30% to 50%).[18] Maternal HSV antibody status before delivery appears to reduce the probability of transmission to infants and the severity of neonatal infection.[19,20] Genital shedding of HSV at delivery and presence of a fetal scalp monitor electrode increase the risk of transmission, as does prolonged rupture of membranes (>6 hours), probably because of ascending HSV infection from the cervix. Importantly, mothers of neonates with active HSV disease often do not have a clinical history of either past genital HSV infection or incident genital lesions, as maternal infection is frequently asymptomatic.[21,22]

HSV co-infection in pregnant women with HIV is not uncommon because both viral infections share risk factors (race, socioeconomic status, and number of sexual partners). Genital HSV-2 was detected by PCR in 23% to 31% of HSV-seropositive women with HIV at the time of delivery, compared with 9% to 12% of HSV-seropositive pregnant women without HIV.[16,23] Shedding is greatest when the CD4 T lymphocyte (CD4) count is low and/or the patient is not receiving ART.[15,24] However, there is no evidence that *in utero* HSV infection of the fetus occurs more frequently in pregnant women with HIV/HSV-2 co-infection, or that infants born to these women are at increased risk of perinatal (intrapartum) HSV infection. In the general population, the neonatal HSV infection rate is 1 case per 2,000 to 10,000 deliveries, indicating that neonatal HSV will be observed rarely at clinics caring for co-infected pregnant women.[17,25]

Numerous studies have shown that co-infection with genital HSV-2 in adults is associated with higher titers of HIV RNA in plasma and genital secretions; HSV-2-seropositivity increases the risk of HIV transmission to sexual partners, even in the absence of genital ulcer disease.[26,27] Three studies suggest that maternal HSV-2 co-infection increases the risk of intrapartum HIV transmission.[28-30]

Clinical Manifestations

In most immunologically competent children outside of the neonatal period, HSV infection causes minimal signs and symptoms and is often unrecognized as a distinct illness. Up to one third of all immunocompetent children may develop a characteristic orolabial syndrome (primary gingivostomatitis), usually from HSV-1 infection, which leads to fever, irritability, tender submandibular lymphadenopathy, and superficial, painful ulcers on the gingival and oral mucosa and perioral skin.[31,32] HSV viremia occurs in approximately one- third of patients with primary herpetic gingivostomatitis.[33] In addition, HSV is a common cause of severe posterior pharyngitis in older children and adolescents.[34,35] Children with advanced HIV infection may have primary infection with multiple lesions that are atypical in appearance and delayed in healing.[36] Very rarely, disseminated HSV with visceral involvement (including liver, adrenals, lung, and brain) and generalized skin lesions occurs in individuals with HIV.[37] A small number of recurrent perioral or perinasal vesicles ("cold sores" or "fever blisters") that heal quickly can occur intermittently in both healthy children and children with HIV throughout their lives, but those with AIDS are at risk of frequent recurrences, which can be associated with severe ulcerative disease and symptoms similar to primary HSV infection.[36,38] Children with HIV also may have prolonged shedding of HSV after both primary and reactivation infection. HSV esophagitis can occur in severely immunocompromised children. A study in adults found that patients with HIV who have HSV esophagitis often lack evidence of oral HSV infection.[39] Prolonged cutaneous HSV infection and organ involvement are AIDS-indicator conditions. However, these illnesses are uncommon in children with HIV in the era of ART, with a documented incidence rate of systemic HSV of only 0.30 per 100 child-years.[40,41]

Genital infection is the most common manifestation of HSV-2 infection in sexually active adolescents. Most primary infections are asymptomatic or subclinical in adolescents who are not HIV infected. Symptomatic disease is characterized by painful, ulcerative lesions on the perineum, penis, labia, and vaginal/urethral mucosae. Mucosal disease often is accompanied by dysuria and/or vaginal or urethral discharge. Inguinal lymphadenopathy is common with perineal disease during primary infection.[42] Frequent recurrences and delayed healing are more likely in severely immunosuppressed patients. Severe HSV proctitis and perianal infections occur in, but are not limited to, patients who practice receptive anal intercourse.[43,44]

HSV keratitis and herpetic whitlow in patients with HIV are similar in presentation to these diseases in individuals without HIV, but may be more severe. Acute retinal necrosis and progressive outer retinal necrosis are rare sight-threatening complications that occur more frequently in immunocompromised individuals.[45,46] HSV encephalitis occurs in patients with HIV, but is not more frequent or more severe than in individuals without HIV and has similar signs and symptoms.[47,48]

Neonatal HSV infection in infants born to mothers with HIV and HSV is similar in presentation to that seen in infants of mothers with HSV alone. Neonatal HSV can appear as disseminated multiorgan disease, localized disease of the central nervous system (CNS), or disease localized to the skin, eyes, and mouth.[49] Vesicular rash occurs in only approximately 60% of infants with CNS or disseminated disease.[17,49,50]

Diagnosis

The clinical diagnosis of HSV infection is based on the typical location and appearance of vesicles and ulcers. The virus is readily isolated in tissue culture within 1 to 3 days, especially when samples are from first episode infections or are obtained early after the appearance of recurrent lesions

(especially when vesicles are present). Speed and sensitivity of diagnosis are maximized with the shell vial method, which combines centrifugation onto coverslips and staining with fluorescein-conjugated monoclonal antibodies after 24 hours to detect synthesis of early-appearing HSV proteins. Detection of HSV DNA by PCR is very sensitive and specific and is the gold-standard method for diagnosis of HSV infection.[51,52] DNA PCR may be especially useful when assessing skin lesions that are recurrent or are being evaluated long after their appearance. In these cases, the HSV DNA remains in the healing lesions and scabs, even though HSV can no longer be cultured. PCR of mucosal and cutaneous sites in neonatal HSV disease has not been evaluated systematically, and culture of those sites in this population remains the standard of care until such comparative studies are completed. Direct immunofluorescence for HSV antigen can be performed on cells scraped from skin, conjunctiva, or mucosal lesions.[53] The sensitivity of this method may be less than 75%, often because it is difficult to obtain evaluable specimens, but the results are usually available the same day.

The preferred diagnostic method for evaluation of children with suspected HSV meningoencephalitis is detection of HSV DNA in the cerebrospinal fluid (CSF), because cultures of CSF are usually negative. Sensitivity of HSV PCR is generally considered to be ≥95% for CSF samples, especially if the samples are obtained more than 3 days after onset of herpes encephalitis.[48,54] In one study of participants with brain biopsy-proven HSV encephalitis, the sensitivity of HSV PCR was 98%.[55] In a report of 15 patients being treated for proven HSV encephalitis, the CSF HSV PCR remained positive for a mean of 10 days after neurologic symptom onset.[56] In neonatal CNS HSV disease, CSF PCR has been reported to have a sensitivity of 75% to 100% and a specificity of 71% to 100%.[48,57] HSV PCR of blood may be used adjunctively in the diagnosis of HSV infection in neonates and other at-risk populations, but its sensitivity remains to be fully defined.[20,58] Definitive diagnosis of HSV esophagitis requires endoscopy with biopsy. Histologic evidence of HSV includes multinucleated giant cells with intranuclear viral inclusions, but diagnosis is established by staining the biopsy with HSV-specific monoclonal antibodies and/or culture or PCR of the tissue.

The rapid onset of poor vision, eye pain, and/or red eye (especially if red eye is associated with decreased vision or pain) should prompt a referral to an ophthalmologist, because these symptoms may be caused by herpesviruses or other pathogens that require specialized diagnostic testing (including fluorescein staining to detect characteristic dendritic corneal ulceration, advanced fundoscopic examination, and sampling of vitreous humor for PCR) and treatment approaches.

Typing of HSV isolates (or genotyping of amplicons) can provide prognostic information. For example, the frequency of recurrence after genital HSV-1 infection in patients without HIV is significantly less than after HSV-2 infection.[59,60]

Prevention Recommendations

Preventing Exposure

Exposure to HSV-1 is frequent in childhood. Although avoiding direct contact with secretions from adult caretakers, siblings, or other close contacts with active herpes labialis is intuitive, it is likely that most infections result from unrecognized exposure to the frequent asymptomatic shedding of HSV by individuals with prior infection.

Male condoms are effective in preventing many sexually transmitted diseases, including HIV.[61,62] When used consistently and correctly, male latex condoms reduce the risk of type 2 genital herpes.[63]

An early study in participants in an HSV vaccine trial demonstrated some protection against HSV infection with condom use, which varied with sex and frequency of sexual activity.[64] A similar, but larger trial demonstrated a 26% reduction in HSV-2 genital infection, but not in HSV-1 infection, with condom use.[65] Protection was related to the proportion of sex acts that were protected with a condom. In a pooled analysis of 6 studies, condom use reduced the risk of HSV-2 acquisition by 30%, and the risk of HSV-2 acquisition increased steadily with each unprotected sex act.[63] A separate analysis of the pooled data estimated that the odds of HSV-2 acquisition with each sexual act were 3.6%, 2.7%, and 0% when condoms were never used, sometimes used, or always used, respectively.[66]

Individuals with HIV should use latex condoms consistently and correctly during sexual intercourse to protect sexual partners and reduce (not eliminate) the risk of acquiring HSV and other sexually transmitted pathogens. They should specifically avoid sexual contact when herpetic lesions (genital or orolabial) are evident. However, most genital herpes infections are transmitted by genital-genital or oral-genital contact from asymptomatic shedding of HSV when their partners are not experiencing a clinical recurrence or are unaware that they are infected. Condoms will not protect against orogenital transmission and infection transmitted prior to penetration.

Administration of chronic suppressive therapy to individuals with HIV and HSV to reduce clinical recurrences also reduces HSV-2 transmission to susceptible HSV-discordant partners without HIV by 25% to 75% and can reduce HSV shedding in patients with HIV/HSV co-infection.[67-71] Although these reductions in transmission and shedding are less than reductions in clinical disease observed with suppressive therapy, when administered to prevent clinical recurrences, suppressive therapy may thus limit spread to sexual partners. All HSV-active antivirals are equally effective in reducing transmission, but twice-daily dosing may be superior to a larger once-daily dose.[69] ART also reduces the frequency of asymptomatic HSV shedding.[15]

Transmission of HSV to fetuses and neonates born to pregnant women with HSV/HIV coinfection can occur, but the likelihood is low. Effective ART regimens may decrease, but not prevent, maternal genital HSV shedding and recurrence of genital lesions.[15] Use of acyclovir or valacyclovir near term suppresses genital HSV outbreaks and shedding in late pregnancy in women with recurrent genital herpes who do not have HIV and reduces the need for cesarean delivery for recurrent HSV.[72] Although the study demonstrating these results had insufficient sample size to determine the effect of prophylaxis on neonatal infection, the American Congress of Obstetricians and Gynecologists (ACOG) recommends that pregnant women with recurrent genital herpes who do not have HIV be offered suppressive antiviral therapy at or beyond 36 weeks of gestation.[73] The safety and efficacy of this strategy have not been evaluated in women with HIV/HSV-2 coinfection, who may have less HSV-2-specific antibody and/or T-cell function and are more likely to have both symptomatic and asymptomatic reactivation of genital HSV. Currently, there is not sufficient data in this population on which to base a specific recommendation regarding this strategy. Importantly, neonatal HSV disease can occur following delivery among women on suppressive antiviral therapy,[74] illustrating that protective effects of maternal suppression are not absolute. Elective cesarean delivery, preferably before rupture of membranes, is recommended for all women, both those with and without HIV, who have active genital HSV lesions at the onset of labor.[75-77]

Preventing Disease

Antiviral prophylaxis before or after potential sexual exposure to HSV has been used successfully to prevent HSV acquisition but has not been studied in patients with HIV and **is not recommended.**[78]

Treatment Recommendations

Treating Disease

Acyclovir is the drug of choice for treatment of local and disseminated HSV in infants and children, regardless of HIV-infection status. Neonatal HSV disease should be treated with intravenous (IV) acyclovir (20 mg/kg body weight three times a day) administered for at least 21 days for CNS and disseminated disease and for 14 days for disease localized to the skin, eyes, and mouth.[79] IV acyclovir therapy should not be discontinued in neonates with CNS disease unless a repeat CSF HSV DNA PCR assay at or after 21 days of treatment is negative.

Treatment of HSV encephalitis or disseminated HSV is the same for children and adolescents with and without HIV. IV acyclovir is the drug of choice. Beyond the neonatal period, HSV encephalitis should be treated for 21 days (10–15 mg/kg body weight three times a day, with dose determined by age and body size).[47,48]

Children and adolescents with severe mucocutaneous HSV lesions or organ involvement (e.g., esophagitis) should receive IV acyclovir (5–10 mg/kg per dose every 8 hours).[80-82] Patients with severe mucocutaneous lesions can be changed to oral antiviral therapy after their lesions have begun to regress. Duration of therapy will depend on the rate and character of healing, but therapy should be continued until all lesions have completely healed. Failure to heal, or a marked delay or change in rate of healing, should raise concern for acyclovir resistance.[83,84]

Oral acyclovir, valacyclovir, or famciclovir are used to treat genital HSV episodes, generally for periods of 5 to 14 days. First-episode genital (or orolabial) lesions in HIV-infected children or adolescents can be treated with oral acyclovir for 7 to 10 days as indicated by the response to therapy.[82,85,86] Patients with recurrent mucocutaneous lesions, if treated, generally receive oral acyclovir for 5 days.

Sufficient information exists to support the use of valacyclovir in children, especially given its 2- to 3-fold improved bioavailability as compared to acyclovir, at a dose of 20 to 25 mg/kg body weight administered 2 to 3 times a day.[87] Lower doses may be insufficient for children weighing less than 20 kg.[88-90] No pediatric formulation is available and valacyclovir can generally only be used for children old enough to swallow the large tablets, although crushed valacyclovir tablets can be used to make an extemporaneous suspension with reliable bioavailability and shelf life following instructions that are included in the U.S. Food and Drug Administration (FDA) Package Insert.[89,91] A sprinkle formulation of famciclovir is available for children who are unable to swallow the available pill formulation or who are too small for available pills. A schedule for weight-adjusted dosing is available to inform dosing of small children.[92] Because of their improved bioavailability, valacyclovir and famciclovir administered at higher doses for only 1 to 3 days often is sufficient to manage recurrent genital HSV infection in HIV-uninfected adults, and these regimens have been used safely in HIV-uninfected children.[93,94] However, these short regimens have not been recommended for HIV-infected adolescents and adults.[82]

Treatment for acute retinal disease caused by HSV should be guided by an ophthalmologist. HIV-infected patients with acute retinal necrosis should be on ART and receive IV acyclovir (10–15 mg/kg body weight IV every 8 hours for 10–14 days), followed by prolonged (i.e., 4–6 weeks) oral therapy, such as with valacyclovir or acyclovir.[95] HSV keratoconjunctivitis is usually treated with topical trifluridine or ganciclovir, although many experts recommend adding oral therapy.[96] Because

of potential corneal toxicity of topical therapy, close follow-up by an ophthalmologist is recommended and duration of therapy should be individualized.

Monitoring and Adverse Events

Primary toxicities of acyclovir are phlebitis (when administered IV), renal toxicity, nausea, vomiting, and rash. Toxicities are similar for valacyclovir and famciclovir, except for phlebitis. In infants receiving high- dose acyclovir for neonatal disease, neutropenia (defined as absolute neutrophil count <1,000/mm^3) occurs in approximately 20% of treated neonates.[79] Among severely ill children who were HIV-uninfected and received high-dose IV acyclovir, renal injury or failure was observed in >10% of patients.[97] It is recommended that renal function be determined at initiation of IV acyclovir treatment and at least once weekly for the duration of treatment, particularly in those who have underlying renal dysfunction and are receiving prolonged therapy. If possible, avoid other nephrotoxic drugs. IV acyclovir must be diluted adequately and administered slowly over 1 to 2 hours. Since acyclovir is excreted primarily by the kidney, dose adjustment based on creatinine clearance is needed in patients with renal insufficiency or renal failure.

Managing Treatment Failure

Resistance of HSV to acyclovir occurs in 5% to 10% of immunocompromised patients.[98] This results from the mutation frequency of HSV, the virostatic nature of acyclovir, and the inadequacy of HSV-specific cell- mediated immunity to rapidly clear the HSV infection. Resistance to antiviral drugs should be suspected if systemic involvement and skin lesions do not begin to resolve within 5 to 7 days after initiation of therapy, skin lesions are atypical in appearance, or satellite lesions appear after 3 to 4 days of therapy. If possible, a lesion culture should be obtained and if virus is isolated, susceptibility testing performed to confirm resistance. This may be difficult to arrange, and results may not be readily available. Thus, the decision to change therapy is often based on clinical observations. All acyclovir-resistant HSV strains are resistant to valacyclovir, and it is very rare that they are sensitive to famciclovir. The therapeutic choice for acyclovir- resistant herpes is foscarnet.[82,83,99,100] Foscarnet has significant nephrotoxic potential; up to 30% of patients experience increases in serum creatinine levels. It also causes serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) in many patients, and secondary seizures or cardiac dysrhythmias can occur. For patients receiving foscarnet, complete blood count, serum electrolytes, and renal function should be monitored twice weekly during induction therapy and once weekly thereafter. Infusing foscarnet after saline fluid loading can minimize renal toxicity. Doses should be modified in patients with renal insufficiency.

IV cidofovir is recommended for patients with HSV resistant to acyclovir and foscarnet.[82,83] For disease limited to a small number of indolent, non-healing lesions, topical formulations of trifluridine, foscarnet, and cidofovir have been used successfully, although this will require local preparation of the topical formulations and may require prolonged application for 21 to 28 days or longer.[101]

Preventing Recurrence

Administration of oral acyclovir prophylaxis (suppressive therapy) for 6 months can prevent cutaneous recurrences of HSV after neonatal disease of the CNS or skin, eyes, and mouth in infants without HIV and is associated with better neurodevelopmental outcome in those with CNS disease.[102]

Because recurrent episodes of mucocutaneous HSV disease can be treated successfully, chronic prophylaxis with acyclovir or other available antivirals against HSV is not required for patients who develop HSV infection beyond the neonatal period. Effective ART may decrease recurrences. Children who have frequent, severe, or troubling recurrences (i.e., 4 to 6 severe episodes a year) can be given daily prophylaxis with oral acyclovir; daily valacyclovir or famciclovir also are options for prophylaxis in adolescents.[69,82] Prophylaxis may be desired not only because recurrences may be especially problematic in patients with severe immune suppression, but also for cosmetic or psychosocial reasons. Use of suppressive antiviral drugs against HSV in adults reduces recurrences by 30% to 60%, and in adults with HIV receiving ART, symptomatic recurrences are reduced by 60% to 75%.[67,68,103]

Because corneal clouding can occur due to the stromal reaction of recurrent keratoconjunctivitis, many ophthalmologists use acyclovir prophylaxis to reduce the frequency of ocular recurrences. However, resistance to acyclovir has been reported in this circumstance in patients without HIV.[104]

Discontinuing Secondary Prophylaxis

Patients receiving prophylactic therapy should be evaluated annually for the need to continue prophylaxis. Cessation of secondary prophylaxis will be determined by the level of immune reconstitution, frequency and severity of recurrences, individual tolerance of recurrent episodes, and location of recurrence (e.g., recurrent keratitis may require longer prophylaxis because of risk of vision-impairing disease).

Recommendations

Primary Prevention

I. Will using condoms, compared to not using condoms, prevent HSV infection in sexually active adolescents and young adults with HIV?

- Condoms should be used to prevent HSV (and other sexually transmitted diseases) in adolescents and young adults with HIV **(strong; low)**. The data regarding the level of protection provided by condoms are very limited for individuals with HIV in general, and for youth specifically.
- Male condoms are effective in preventing many sexually transmitted diseases, including HIV. A large observational trial on condom use and HSV acquisition demonstrated a 26% reduction in HSV-2 genital infection, but not in HSV-1 infection.[65] A pooled analysis of 6 similar studies concluded that condom usage resulted in a 30% lower risk of HSV-2 acquisition as compared to no condom use.[63,66] Patients with HIV should use latex condoms consistently and correctly during sexual intercourse to reduce the risk of acquiring HSV and other sexually transmitted pathogens and to protect sexual partners.

Secondary Prevention

II. Will adolescents and young adults with HIV who have recurrent genital HSV infection benefit from suppressive anti-HSV antiviral therapy as compared to not using suppressive therapy?

- Adolescents and young adults with HIV who suffer severe, frequent, and/or troubling recurrent genital HSV infection will benefit from anti-HSV suppression therapy **(strong; moderate)**.
- Placebo-controlled trials demonstrated that antiviral drugs against HSV, administered for recurrent HSV disease in adults with HIV who are receiving ART, reduced symptomatic recurrences by 60% to 75%. This is an option for patients with frequent, severe, or troubling HSV recurrences. Chronic suppressive therapy in individuals with HSV also reduced HSV-2 transmission to susceptible partners without HIV by 25% to 75%.[67-69]

Treatment

III. Should children and adolescents with HIV with severe primary or recurrent HSV (genital or orolabial) infection receive IV acyclovir as compared to not receiving IV antiviral therapy?

- Children and youth with HIV who have severe mucocutaneous HSV infections should be treated with IV acyclovir. When improvement is noted, they can be switched to oral therapy until healing is complete **(strong; moderate)**.
- Placebo-controlled trials in children and youth with immunocompromising conditions (other than HIV infection) indicate that those with severe mucocutaneous HSV lesions or organ involvement benefitted from IV acyclovir.[80,81] Patients with severe mucocutaneous lesions can be switched to oral antiviral therapy after their lesions have begun to regress. Duration of therapy will depend on the rate and character of healing, but therapy should be continued until lesions have completely healed. Failure to heal, or a marked delay or change in rate of healing, should raise concern for acyclovir resistance.

IV. Should children and adolescents with HIV be treated with oral acyclovir, valacyclovir, or famciclovir for non-severe primary episodes or recurrent episodes of orolabial or genital HSV (compared with no antiviral therapy)?

- Oral anti-HSV drugs will shorten the duration and reduce the severity of non-severe HSV infections in children and adolescents with HIV. Valacyclovir and famciclovir have superior pharmacokinetics **(strong; moderate)**.
- Controlled trials in children without HIV and adults with HIV indicate that treatment of first-episode orolabial or genital HSV lesions results in reduction in duration and severity of lesions.[85,86] Recurrent mucocutaneous lesions also benefit from treatment. Because of their improved bioavailability, valacyclovir and famciclovir can be administered less frequently and will achieve higher serum antiviral levels when

compared with acyclovir. Both alternatives have been safely used in children without HIV.[92,93]

V. Is foscarnet the best choice for anti-HSV therapy for children and adolescents with HIV in whom therapy is failing because of acyclovir-resistant HSV?

- Foscarnet is the therapy of choice for acyclovir-resistant HSV **(strong, very low)**. Ideally, the viral isolate should be tested to determine the antiviral resistance pattern.

  Resistance of HSV to acyclovir occurs in 5% to 10% of immunocompromised patients. Resistance to antiviral drugs should be suspected if systemic involvement and skin lesions do not begin to resolve within 5 to 7 days after initiation of therapy. The decision to change therapy often is based on clinical observations because virus isolation and testing for resistance take many days. The therapeutic choice for acyclovir-resistant herpes is foscarnet, based primarily on the sensitivity pattern of HSV isolates from HSV infections unresponsive to acyclovir in immunocompromised patients[99,100] and expert opinion. Patients receiving foscarnet should have electrolytes and renal function monitored twice weekly during induction therapy and once weekly thereafter. The package insert contains an algorithm for drug infusion and dose modification for patients with renal insufficiency.

Dosing Recommendations for Prevention and Treatment of Herpes Simplex Virus Infections

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	None	None	Primary prophylaxis is not indicated.
Secondary Prophylaxis	Mucocutaneous Disease • Acyclovir 20 mg/kg body weight/ dose (maximum 800 mg/dose) by mouth BID Suppressive Therapy After Neonatal HSV Disease (Skin, Eye, Mouth, CNS, or Disseminated Disease) • Acyclovir 300 mg/m^2 body surface area/dose by mouth TID for 6 months	Mucocutaneous Disease, for Adolescents Old Enough to Receive Adult Dosing • Valacyclovir 500 mg by mouth BID, *or* • Famciclovir 500 mg by mouth BID	Secondary Prophylaxis Indicated • Suppressive secondary prophylaxis can be considered for children with severe and recurrent mucocutaneous (oral or genital) disease. Criteria for Discontinuing Secondary Prophylaxis • After a prolonged period (e.g., 1 year) of prophylaxis, consider suspending prophylaxis and determine with the patient whether additional prophylaxis is necessary. Although level of immune reconstitution is a consideration, no specific CD4 threshold has been established.
Treatment	Neonatal CNS or Disseminated Disease • Acyclovir 20 mg/kg body weight IV/ dose every 8 hours for ≥21 days Neonatal Skin, Eye, or Mouth Disease • Acyclovir 20 mg/kg body weight IV/ dose every 8 hours for 14 days CNS or Disseminated Disease in Children Outside the Neonatal Period • Acyclovir 10 mg/kg body weight (up to 15 mg/kg body weight/dose in children <12 years) IV every 8 hours for 21 days	• Valacyclovir is approved for immunocompetent adults and adolescents with first-episode mucocutaneous HSV at a dose of 1 g by mouth BID for 7–10 days; also approved for recurrent herpes labialis in children ≥12 years using two, 2-g doses by mouth separated by 12 hours as single-day therapy. • Recurrent genital HSV can be treated with valacyclovir 500 mg BID for 3 days or 1 g by mouth daily for 5 days. • Immunocompetent adults with recurrent herpes labialis can be treated with famciclovir, 1 g/dose by mouth BID for 1 day. • Famciclovir is approved to treat primary genital HSV in immunocompetent adults at a dose of 250 mg/dose by mouth TID for 7–10 days.	For Neonatal CNS Disease • Repeat CSF HSV DNA PCR should be performed on days 19 to 21 of therapy. If the repeat CSF HSV DNA PCR is positive, continue IV acyclovir for an additional week, repeating the CSF HSV DNA PCR again near the end of extended treatment. Acyclovir should not be stopped until a repeat CSF HSV DNA PCR is negative. • There is no pediatric preparation of valacyclovir (although crushed capsules can be used to make a suspension according to specific instructions provided in the U.S. FDA package insert) and data on dosing in children are limited. Valacyclovir can be used by adolescents able to receive adult dosing.

	Moderate to Severe Symptomatic Gingivostomatitis • Acyclovir 5–10 mg/kg body weight/ dose IV every 8 hours. Patients can be switched to oral therapy after lesions have begun to regress and therapy continued until lesions have completely healed. Mild Symptomatic Gingivostomatitis • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 7–10 days Recurrent Herpes Labialis • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth QID for 5 days For First-Episode Genital Herpes (Adults and Adolescents): • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 7–10 days Recurrent Genital Herpes (Adults and Adolescents) • Acyclovir 20 mg/kg body weight (maximum 400 mg/dose) dose by mouth TID for 5 days Children with HSV Keratoconjunctivitis • Often treated with topical trifluridine (1%) or ganciclovir (0.15%) applied as 1–2 drops 5 times daily. Many experts add oral acyclovir to the topical therapy. Children with ARN • For children old enough to receive adult dose, acyclovir	• Recurrent genital HSV is treated with famciclovir 1 g/dose by mouth BID at a 12-hour interval for 2 doses. • Famciclovir is approved for use in HIV-infected adults and adolescents with recurrent mucocutaneous HSV infection at a dose of 500 mg/dose by mouth BID for 7 days. Acyclovir-Resistant HSV Infection • Foscarnet 40 mg/kg body weight/ dose given IV every 8 hours (or 60 mg/kg body weight/dose IV every 12 hours) should be administered slowly over the course of 2 hours (i.e., no faster than 1 mg/kg/ minute).	• Famciclovir is available in a sprinkle formulation with weight-adjusted dosing. Famciclovir can be used by adolescents able to receive adult dosing. Alternative and Short-Course Therapy in Immunocompromised Adults with Recurrent Genital Herpes • Acyclovir 800 mg per dose by mouth BID for 5 days • Acyclovir 800 mg per dose by mouth TID for 2 days Note: Consultation with an ophthalmologist experienced in managing herpes simplex infection involving the eye and its complications in children is strongly recommended when ocular disease is present.

	10–15 mg/kg body weight/dose IV every 8 hours for 10–14 days, followed by oral valacyclovir 1 g/dose TID for 4–6 weeks As an alternative, oral acyclovir 20 mg/kg body weight/dose QID for 4–6 weeks after IV acyclovir for 10–14 days		

Key to Acronyms: ARN = acute retinal necrosis; BID = twice a day; CD4 = CD4 T lymphocyte; CNS = central nervous system; FDA = Food and Drug Administration; CSF = cerebrospinal fluid; HSV = herpes simplex virus; IV = intravenous; PCR = polymerase chain reaction; QID = four times a day; TID = three times a day

References

1. Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. *Sex Transm Dis*. 2003;30(10):797-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14520181.

2. Samra Z, Scherf E, Dan M. Herpes simplex virus type 1 is the prevailing cause of genital herpes in the Tel Aviv area, Israel. *Sex Transm Dis*. 2003;30(10):794-796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14520180.

3. Ryder N, Jin F, McNulty AM, Grulich AE, Donovan B. Increasing role of herpes simplex virus type 1 in first-episode anogenital herpes in heterosexual women and younger men who have sex with men, 1992-2006. *Sex Transm Infect*. 2009;85(6):416-419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19273479.

4. Bernstein DI, Bellamy AR, Hook EW 3rd, et al. Epidemiology, clinical presentation, and antibody response to primary infection with herpes simplex virus type 1 and type 2 in young women. *Clin Infect Dis*. 2013;56(3):344-351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23087395.

5. Xu F, Lee FK, Morrow RA, et al. Seroprevalence of herpes simplex virus type 1 in children in the United States. *J Pediatr*. 2007;151(4):374-377. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17889072.

6. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA*. 2006;296(8):964-973. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16926356.

7. Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999-2010. *J Infect Dis*. 2014;209(3):325-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24136792.

8. Stanberry LR, Rosenthal SL, Mills L, et al. Longitudinal risk of herpes simplex virus (HSV) type 1, HSV type 2, and cytomegalovirus infections among young adolescent girls. *Clin Infect Dis*. 2004;39(10):1433-1438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15546077.

9. Weiss H. Epidemiology of herpes simplex virus type 2 infection in the developing world. *Herpes*. 2004;11 Suppl 1:24A-35A. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15115627.

10. Raguin G, Malkin JE. Genital herpes: epidemiology and pathophysiology. Update and new perspectives. *Ann Med Interne (Paris)*. 1997;148(8):530-533. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9538399.

11. Lafferty WE. The changing epidemiology of HSV-1 and HSV-2 and implications for serological testing. *Herpes*. 2002;9(2):51-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12106513.

12. Mark KE, Wald A, Magaret AS, et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J Infect Dis*. 2008;198(8):1141-1149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18783315.

13. van Velzen M, Ouwendijk WJ, Selke S, et al. Longitudinal study on oral shedding of herpes simplex virus 1 and varicella-zoster virus in individuals infected with HIV. *J Med Virol*. 2013;85(9):1669-1677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23780621.

14. Miller CS, Danaher RJ. Asymptomatic shedding of herpes simplex virus (HSV) in the oral cavity. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008;105(1):43-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17703961.

15. Posavad CM, Wald A, Kuntz S, et al. Frequent reactivation of herpes simplex virus among HIV-1-infected patients treated with highly active antiretroviral therapy. *J Infect Dis*. 2004;190(4):693-696. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15272395.

16. Perti T, Nyati M, Gray GE, et al. Frequent genital HSV-2 shedding among women during labor in Soweto, South Africa. *Infectious Diseases in Obstetrics and Gynecology*. 2014;2014(105):291. Available at: http://www.hindawi.com/journals/idog/2014/258291/.

17. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med*. 2009;361(14):1376-1385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19797284.

18. Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus infections. *Pediatr Clin North Am*. 2013;60(2):351-365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23481105.

19. Ashley RL, Dalessio J, Burchett S, et al. Herpes simplex virus-2 (HSV-2) type-specific antibody correlates of protection in infants exposed to HSV-2 at birth. *J Clin Invest*. 1992;90(2):511-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1322941.

20. Kimberlin DW. Herpes simplex virus infections in neonates and early childhood. *Semin Pediatr Infect Dis*. 2005;16(4):271-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16210107.

21. Tookey P, Peckham CS. Neonatal herpes simplex virus infection in the British Isles. *Paediatr Perinat Epidemiol*. 1996;10(4):432-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8931058.

22. Whitley R, Davis EA, Suppapanya N. Incidence of neonatal herpes simplex virus infections in a managed-care population. *Sex Transm Dis*. 2007;34(9):704-708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17413535.

23. Patterson J, Hitti J, Selke S, et al. Genital HSV detection among HIV-1-infected pregnant women in labor. *Infect Dis Obstet Gynecol*. 2011;2011:157680. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21527986.

24. Mostad SB, Kreiss JK, Ryncarz A, et al. Cervical shedding of herpes simplex virus and cytomegalovirus throughout the menstrual cycle in women infected with human immunodeficiency virus type 1. *Am J Obstet Gynecol*. 2000;183(4):948- 955. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11035345.

25. Flagg EW, Weinstock H. Incidence of neonatal herpes simplex virus infections in the United States, 2006. *Pediatrics* 2011;127(1):e1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21149432.

26. Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis*. 2002;185(1):45-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11756980.

27. Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS*. 2006;20(1):73-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16327322.

28. Chen KT, Segu M LL, Kuhn L, Carter RJ, Bulterys M, et al. Genital herpes simplex virus infection and perinatal transmission of human immunodeficiency virus. *Obstet Gynecol*. 2005;106(6):1341-1348.

29. Cowan FM, Humphrey JH, Ntozini R, Mutasa K, Morrow R, Iliff P. Maternal Herpes simplex virus type 2 infection, syphilis and risk of intra-partum transmission of HIV-1: results of a case control study. *AIDS*. 2008;22(2):193-201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18097221.

30. Drake AL, John-Stewart GC, Wald A, et al. Herpes simplex virus type 2 and risk of intrapartum human immunodeficiency virus transmission. *Obstet Gynecol*. 2007;109(2 Pt 1):403-409. Available at: http://www.ncbi.nlm. nih.gov/pubmed/17267842.

31. Amir J, Harel L, Smetana Z, Varsano I. The natural history of primary herpes simplex type 1 gingivostomatitis in children. *Pediatr Dermatol*. 1999;16(4):259-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10469407.

32. Arvin AM. Chapter 163: Herpes simplex 1 & 2. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL, eds. *Textbook of Pediatric Infectious Disease*, 5th Edition. Philadelphia: Saunders; 2004:1884-1912.

33. Harel L, Smetana Z, Prais D, et al. Presence of viremia in patients with primary herpetic gingivostomatitis. *Clin Infect Dis*. 2004;39(5):636-640. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15356775.

34. Glezen WP, Fernald GW, Lohr JA. Acute respiratory disease of university students with special reference to the etiologic role of herpesvirus hominis. *Am J Epidemiol*. 1975;101(2):111-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/164768.

35. McMillan JA, Weiner LB, Higgins AM, Lamparella VJ. Pharyngitis associated with herpes simplex virus in college students. *Pediatr Infect Dis J*. 1993;12(4):280-284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8387178.

36. Wananukul S, Deekajorndech T, Panchareon C, Thisyakorn U. Mucocutaneous findings in pediatric AIDS related to degree of immunosuppression. *Pediatr Dermatol*. 2003;20(4):289-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12869145.

37. Lee L, Agwu A, Hutton N. Severe primary HSV-2 in a perinatal HIV-infected woman with advanced immunosuppression. *Case Rep Med*. 2012;2012:346039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22899940.

38. Salvini F, Carminati G, Pinzani R, Carrera C, Rancilio L, Plebani A. Chronic ulcerative herpes simplex virus infection in HIV-infected children. *AIDS Patient Care STDS*. 1997;11(6):421-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11361863.

39. Genereau T, Lortholary O, Bouchaud O, et al. Herpes simplex esophagitis in patients with AIDS: report of 34 cases. The cooperative study group on herpetic esophagitis in HIV infection. *Clin Infect Dis*. 1996;22(6):926-931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8783688.

40. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *JAMA*. 2006;296(3):292-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16849662.

41. Mirani G, Williams PL, Chernoff M, et al. Changing trends in complications and mortality rates among US youth and young adults with HIV infection in the era of combination antiretroviral therapy. *Clin Infect Dis*. 2015;61(12):1850- 1861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26270680.

42. Kimberlin DW, Rouse DJ. Clinical practice. genital herpes. *N Engl J Med*. 2004;350(19):1970-1977. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15128897.

43. Krone MR, Wald A, Tabet SR, Paradise M, Corey L, Celum CL. Herpes simplex virus type 2 shedding in human immunodeficiency virus-negative men who have sex with men: frequency, patterns, and risk factors. *Clin Infect Dis*. 2000;30(2):261-267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10671325.

44. Bissessor M, Fairley CK, Read T, Denham I, Bradshaw C, Chen M. The etiology of infectious proctitis in men who have sex with men differs according to HIV status. *Sex Transm Dis*. 2013;40(10):768-770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24275725.

45. Ormerod LD, Larkin JA MC, et al. Rapidly progressive herpetic retinal necrosis: a blinding disease characteristic of advanced AIDS. *Clin Infect Dis* 1998;26(1):34-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9455507.

46. Purdy KW, Heckenlively JR, Church JA, Keller MA. Progressive outer retinal necrosis caused by varicella-zoster virus in children with acquired immunodeficiency syndrome. *Pediatr Infect Dis J*. 2003;22(4):384-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12712978.

47. Whitley RJ, Kimberlin DW. Herpes simplex encephalitis: children and adolescents. *Semin Pediatr Infect Dis*. 2005;16(1):17-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15685145.

48. De Tiege X, Rozenberg F, Heron B. The spectrum of herpes simplex encephalitis in children. *Eur J Paediatr Neurol*. 2008;12(2):72-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17870623.

49. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics* 2001;108(2):223-229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11483781.

50. Kimberlin DW. Herpes simplex virus infections of the newborn. *Semin Perinatol*. 2007;31(1):19-25. Available at: http:// www.ncbi.nlm.nih.gov/pubmed/17317423.

51. Cone RW, Hobson AC, Palmer J, Remington M, Corey L. Extended duration of herpes simplex virus DNA in genital lesions detected by the polymerase chain reaction. *J Infect Dis*. 1991;164(4):757-760. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1654360.

52. Kimberlin DW. Diagnosis of herpes simplex virus in the era of polymerase chain reaction. *Pediatr Infect Dis J*. 2006;25(9):841-842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16940845.

53. Slomka MJ, Emery L, Munday PE, Moulsdale M, Brown DW. A comparison of PCR with virus isolation and direct antigen detection for diagnosis and typing of genital herpes. *J Med Virol*. 1998;55(2):177-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9598940.

54. Weil AA, Glaser CA, Amad Z, Forghani B. Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. *Clin Infect Dis*. 2002;34(8):1154-1157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11915008.

55. Lakeman FD, Whitley RJ. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis*. 1995;171(4):857-863. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7706811.

56. Kimura H, Aso K, Kuzushima K, Hanada N, Shibata M, Morishima T. Relapse of herpes simplex encephalitis in children. *Pediatrics* 1992;89(5 Pt 1):891-894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1315949.

57. Pinninti SG, Kimberlin DW. Management of neonatal herpes simplex virus infection and exposure. *Arch Dis Child Fetal Neonatal Ed*. 2014;99(3):F240-244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24589428.

58. Melvin AJ, Mohan KM, Schiffer JT, et al. Plasma and cerebrospinal fluid herpes simplex virus levels at diagnosis and outcome of neonatal infection. *J Pediatr*. 2015;166(4):827-833. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25491092.

59. Lafferty WE, Coombs RW, Benedetti J, Critchlow C, Corey L. Recurrences after oral and genital herpes simplex virus infection. Influence of site of infection and viral type. *N Engl J Med*. 1987;316(23):1444-1449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3033506.

60. Engelberg R, Carrell D, Krantz E, Corey L, Wald A. Natural history of genital herpes simplex virus type 1 infection. *Sex Transm Dis*. 2003;30(2):174-177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12567178.

61. Centers for Disease Control and Prevention. Update: barrier protection against HIV infection and other sexually transmitted diseases. *MMWR*. 1993;42(30):589-591, 597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8336689.

62. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev*. 2002(1):CD003255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11869658.

63. Martin ET, Krantz E, Gottlieb SL, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. *Arch Intern Med*. 2009;169(13):1233-1240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19597073.

64. Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA*. 2001;285(24):3100-3106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11427138.

65. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med*. 2005;143(10):707-713. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16287791.

66. Stanaway JD, Wald A, Martin ET, Gottlieb SL, Magaret AS. Case-crossover analysis of condom use and herpes simplex virus type 2 acquisition. *Sex Transm Dis*. 2012;39(5):388-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22504606.

67. Schacker T, Hu HL, Koelle DM, et al. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. A double-blind, placebo-controlled trial. *Ann Intern Med*. 1998;128(1):21-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9424977.

68. DeJesus E, Wald A, Warren T ST, Trottier S, Shahmanesh M, et al. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. *J Infect Dis*. 2003;188(7):1009-1016.

69. Strick LB, Wald A, Celum C. Management of herpes simplex virus type 2 infection in HIV type 1-infected persons. *Clin Infect Dis*. 2006;43(3):347-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16804851.

70. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med*. 2004;350(1):11-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14702423.

71. Conant MA, Schacker TW, Murphy RL, et al. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV- infected individuals: two randomized trials. *Int J STD AIDS*. 2002;13(1):12-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11802924.

72. Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. *Cochrane Database Syst Rev*. 2008(1):CD004946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18254066.

73. Bulletins ACoP. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. No. 82 June 2007. Management of herpes in pregnancy. *Obstetrics and gynecology*. 2007;109(6):1489-1498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17569194.

74. Pinninti SG, Angara R, Feja KN, et al. Neonatal herpes disease following maternal antenatal antiviral suppressive therapy: a multicenter case series. *J Pediatr*. 2012;161(1):134-138 e131-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22336576.

75. American College of Obstetricians and Gynecologists. Management of herpes in pregnancy, ACLG Practice Bulletin 8. Washington, DC.1999.

76. Prober CG, Corey L, Brown ZA, et al. The management of pregnancies complicated by genital infections with herpes simplex virus. *Clin Infect Dis*. 1992;15(6):1031-1038. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1457634.

77. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA*. 2003;289(2):203-209. Available at: http://www. ncbi.nlm.nih.gov/pubmed/12517231.

78. Abdool Karim SS, Abdool Karim Q, Kharsany AB, et al. Tenofovir gel for the prevention of herpes simplex virus type 2 infection. *N Engl J Med*. 2015;373(6):530-539. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26244306.

79. Kimberlin DW, Lin CY, Jacobs RF, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001;108(2):230-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11483782.

80. Mitchell CD, Bean B, Gentry SR, Groth KE, Boen JR, Balfour HH, Jr. Acyclovir therapy for mucocutaneous herpes simplex infections in immunocompromised patients. *Lancet*. 1981;1(8235):1389-1392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6113352.

81. Wade JC, Newton B, McLaren C, Flournoy N, Keeney RE, Meyers JD. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: a double-blind trial. *Ann Intern Med*. 1982;96(3):265-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7036816.

82. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2016. Available at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new

83. Safrin S, Elbeik T, Phan L, et al. Correlation between response to acyclovir and foscarnet therapy and in vitro susceptibility result for isolates of herpes simplex virus from human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 1994;38(6):1246-1250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8092821.

84. Levin MJ, Bacon TH LJ. Resistance of herpes simplex virus infections to nucleoside analogues in HIV-infected patients. *Clin Infect Dis*. 2004;39(Suppl 5):S248-257.

85. Amir J, Harel L, Smetana Z, Varsano I. Treatment of herpes simplex gingivostomatitis with aciclovir in children: a randomised double blind placebo controlled study. *BMJ*. 1997;314(7097):1800-1803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9224082.

86. Paz-Bailey G, Sternberg M, Puren AJ, et al. Improvement in healing and reduction in HIV shedding with episodic acyclovir therapy as part of syndromic management among men: a randomized, controlled trial. *J Infect Dis*. 2009;200(7):1039-1049. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19715417.

87. Kimberlin DW, Jacobs RF, Weller S, et al. Pharmacokinetics and safety of extemporaneously compounded valacyclovir oral suspension in pediatric patients from 1 month through 11 years of age. *Clin Infect Dis*. 2010;50(2):221-228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20014952.

88. Eksborg S, Pal N, Kalin M, Palm C, Soderhall S. Pharmacokinetics of acyclovir in immunocompromized children with leukopenia and mucositis after chemotherapy: can intravenous acyclovir be substituted by oral valacyclovir? *Med Pediatr Oncol*. 2002;38(4):240-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920787.

89. Valtrex [package insert]. GlaxoSmithKline. 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020487s016lbl.pdf

90. Zeng L, Blair EY, Nath CE, et al. Population pharmacokinetics of mycophenolic acid in children and young people undergoing blood or marrow and solid organ transplantation. *Br J Clin Pharmacol*. 2010;70(4):567-579. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20840448.

91. PDR Network. Physicians Desk Reference. 65 ed. 2011. Montvale, NJ: PDR Network, LLC.

92. Saez-Llorens X, Yogev R, Arguedas A, et al. Pharmacokinetics and safety of famciclovir in children with herpes simplex or varicella-zoster virus infection. *Antimicrob Agents Chemother*. 2009;53(5):1912-1920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19273678.

93. Block SL, Yogev R, Waldmeier F, Hamed K. Safety and pharmacokinetics of a single 1500-mg dose of famciclovir in adolescents with recurrent herpes labialis. *Pediatr Infect Dis J*. 2011;30(6):525-528. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21178655.

94. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1-137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26042815.

95. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44 (Suppl 1):S1-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17143845.

96. Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. *Cochrane Database Syst Rev*. 2010(12):CD002898. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21154352.

97. Rao S, Abzug MJ, Carosone-Link P, et al. Intravenous acyclovir and renal dysfunction in children: a matched case control study. *J Pediatr*. 2015;166(6):1462-1468 e1461-1464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25708691.

98. Bacon TH, Levin MJ, Leary JJ, Sarisky RT, Sutton D. Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy. *Clin Microbiol Rev*. 2003;16(1):114-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12525428.

99. Stranska R, Schuurman R, Nienhuis E, et al. Survey of acyclovir-resistant herpes simplex virus in the Netherlands: prevalence and characterization. *J Clin Virol*. 2005;32(1):7-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15572000.

100. Chen Y, Scieux C, Garrait V, et al. Resistant herpes simplex virus type 1 infection: an emerging concern after allogeneic stem cell transplantation. *Clin Infect Dis*. 2000;31(4):927-935. Available at: http://www.ncbi.nlm.nih.gov/ pubmed/11049772.

101. Lateef F, Don PC, Kaufmann M, White SM, Weinberg JM. Treatment of acyclovir-resistant, foscarnet-unresponsive HSV infection with topical cidofovir in a child with AIDS. *Arch Dermatol*. 1998;134(9):1169-1170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9762047.

102. Kimberlin DW, Whitley RJ, Wan W, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. *N Engl J Med*. 2011;365(14):1284-1292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21991950.

103. Le Cleach L, Trinquart L, Do G, et al. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. *Cochrane Database Syst Rev*. 2014;8:CD009036. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25086573.

104. Duan R, de Vries RD, van Dun JM, et al. Acyclovir susceptibility and genetic characteristics of sequential herpes simplex virus type 1 corneal isolates from patients with recurrent herpetic keratitis. *J Infect Dis*. 2009;200(9):1402-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19795980.