



## **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**

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# Herpes Simplex Virus Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

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## Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common, with a seroprevalence of HSV-1 among adults in the United States of approximately 60% and a seroprevalence of HSV-2 among persons aged  $\geq 12$  years of 17%.<sup>1</sup> Approximately 70% of HIV-infected persons are HSV-2 seropositive and 95% are seropositive for either HSV-1 or HSV-2.<sup>2</sup> In most HSV-infected persons, HSV infections are unrecognized clinically. However, regardless of the clinical severity of infection, re-activation on mucosal surfaces occurs frequently and can result in transmission. HSV-2 infection increases the risk of HIV acquisition two- to three-fold, and HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions of coinfecting patients.

## Clinical Manifestations

Oral herpes (e.g., cold sores, fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations include a sensory prodrome in the affected area, rapidly followed by the evolution of lesions from papule to vesicle, ulcer, and crust stages on the lip. The course of illness in untreated patients is 5 to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress.

Genital herpes is the most common manifestation of HSV-2 infection. Typical genital mucosal or skin lesions evolve through stages of papule, vesicle, ulcer, and crust. Ulcerative lesions are usually the only stage observed on mucosal surfaces, but vesicles are commonly seen on genital skin (e.g., the penile shaft, thighs, pubis). Local symptoms might include a sensory prodrome consisting of pain and pruritis. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.<sup>3</sup> These classic manifestations occur in some patients, but most individuals with genital herpes have mild and atypical lesions that are often unrecognized, not brought to medical attention, and cannot reliably be diagnosed by physical examination. In profoundly immunocompromised patients, extensive, deep, nonhealing ulcerations can occur. These lesions have been reported most often in those with CD4 T-lymphocyte (CD4) cell counts of  $< 100$  cells/ $\mu$ L and also may be more commonly associated with acyclovir-resistant HSV.<sup>4</sup>

An episode of genital HSV-1 disease is indistinguishable from genital HSV-2 disease, but genital HSV-1 recurrences and viral shedding occur less often than with genital HSV-2 infection.

Non-mucosal HSV infections, such as HSV keratitis, HSV encephalitis, HSV hepatitis, and herpetic whitlow, are similar in presentation to manifestations observed in HIV-seronegative individuals; disseminated HSV infection is rare, even in profoundly immunosuppressed patients. HSV retinitis manifests as acute retinal necrosis, which can lead rapidly to loss of vision.

## Diagnosis

Because mucosal HSV infections cannot be diagnosed accurately by clinical examination, especially in HIV-seropositive patients, a laboratory diagnosis should be pursued in all cases.<sup>5</sup> Viral culture, HSV DNA Polymerase chain reaction, and HSV antigen detection are available methods for diagnosis of mucocutaneous HSV lesions caused by HSV. Polymerase chain reaction is the most sensitive method. The virus detected in genital lesions should be typed because of the prognostic significance—HSV-1 recurs less frequently than HSV-2 in the genital area. Type-specific serologic assays are commercially available and can be used for diagnosis in asymptomatic individuals or those with atypical lesions. Because of the poor sensitivity and specificity of clinical diagnosis, the extensive interactions between HIV and HSV-2, and the availability of effective therapy for HSV-2, routine type-specific serologic screening for HSV-2 should be considered in

patients seeking care for HIV. Diagnosis of HSV-2 should be accompanied by counseling that includes discussion of the risk of transmitting infection to sex partners. Guidelines for counseling are provided in the 2010 Centers for Disease Control and Prevention sexually transmitted disease treatment guidelines.<sup>5</sup>

## Preventing Exposure

The majority of HIV-infected patients have HSV-1 and HSV-2 infections. However, prevention of acquisition of HSV is important for those who are uninfected. HSV-2-seronegative HIV-infected patients should ask their partners to be tested using type-specific serology before initiating sexual activity, because disclosure of HSV-2 in heterosexual HSV-2-discordant couples was associated with reduced risk of transmission of HSV-2 (**BII**).<sup>6</sup> Consistent use of latex condoms reduced HSV-2 acquisition from women to men and from men to women, and their use should be encouraged for prevention of transmission of HSV-2 and other sexually transmitted pathogens (**AII**).<sup>7,8</sup> HIV-infected individuals should specifically avoid sexual contact when their partners have overt (genital or orolabial) herpetic lesions (**AII**). However, most sexual transmission of HSV occurs during asymptomatic viral shedding.

The use of suppressive antiviral therapy (i.e., valacyclovir 500 mg once daily) in patients with genital herpes reduced HSV-2 transmission to susceptible heterosexual partners by 50%;<sup>9</sup> the effectiveness of this approach in reducing HSV-2 transmission to or from HIV-seropositive patients has not been evaluated.

## Preventing Disease

Prophylaxis with antiviral drugs to prevent primary HSV infection **is not recommended** (**BIII**). The dose, duration, timing, and efficacy of antiviral prophylaxis after known or suspected exposure to HSV have not been evaluated. No vaccine for prevention of HSV infection is available.

## Treating Disease

Patients with HSV infections can be treated with episodic therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences. The management plan for genital HSV-2 disease in HIV-infected individuals should include consideration of several factors, such as frequency and severity of HSV recurrences, the risk of HSV-2 transmission to susceptible partners, and the potential for interactions between HIV and HSV-2 that might result in increased HIV viral load in plasma and genital secretions. Episodic treatment for individual recurrences does not influence the natural history of genital HSV-2 infection and does not reduce the risk of HSV-2 transmission to sex partners, a major concern for patients with genital herpes.

Patients with orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for 5 to 10 days (**AIII**). Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir (**AIII**).<sup>4,10</sup> Patients can be switched to oral antiviral therapy after their lesions have begun to regress. Therapy should be continued until the lesions have completely healed. Genital HSV episodes should be treated with oral valacyclovir, famciclovir, or acyclovir for 5 to 14 days (**AI**). Disseminated disease due to HSV is rare in HIV-seropositive patients, although HSV necrotizing retinitis can occur, which may be difficult to distinguish clinically from retinitis caused by VZV.

## *Special Considerations with Regard to Starting Antiretroviral Therapy*

In most instances, orolabial HSV should not influence the decision about when to start antiretroviral therapy (ART). HIV-infected patients receiving ART who have immune reconstitution often have improvement in the frequency and severity of their clinical episodes of genital herpes. However, immune reconstitution does not reduce the frequency of genital HSV shedding.<sup>11</sup> Chronic cutaneous or mucosal HSV that is refractory to therapy and visceral or disseminated cases of HSV disease (which are uncommon) would be indications to hasten the initiation of ART (**CIII**).

## ***Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome [IRIS])***

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed in patients receiving episodic or suppressive therapy unless they have advanced renal impairment. For patients receiving high-dose IV acyclovir, monitoring of renal function and dose adjustment as necessary are recommended at initiation of treatment and once or twice weekly for the duration of treatment. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported in HIV-infected patients treated with high-dose (8 g/day) valacyclovir, but has not been reported at conventional doses recommended for therapy of HSV infection.<sup>12</sup>

Mucocutaneous lesions that are atypical and occasionally recalcitrant to therapy have been reported in individuals initiating ART and have been attributed to IRIS.<sup>13</sup>

## ***Managing Treatment Failure***

Treatment failure as a result of resistance to anti-HSV drugs should be suspected if lesions do not begin to resolve within 7 to 10 days after initiation of therapy. In immunocompromised patients with suspected acyclovir-resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing done to confirm drug resistance (**AI**).<sup>14</sup> Phenotypic testing of viral isolates has been the gold standard method for assessing HSV resistance; genotypic testing is under development.

The treatment of choice for acyclovir-resistant HSV is IV foscarnet (**AI**).<sup>15,16</sup> IV cidofovir is a potential alternative. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer may be required (**CIII**).

## **Preventing Recurrence**

Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences and is preferred for patients who have severe HSV recurrences or who want to minimize the frequency of recurrences (**AI**).<sup>5,17</sup> Suppressive anti-HSV therapy in HIV-infected individuals also results in a decrease in HIV viral load in plasma and anal and genital secretions and in a lower risk of HIV progression.<sup>18</sup> This regimen does not decrease the risk of HIV transmission to sexual partners.<sup>19</sup> Suppressive therapy for HSV is usually continued indefinitely, without regard for improved CD4 cell count.

The use of daily suppressive therapy (when compared to episodic therapy) was associated with a lower risk of development of acyclovir-resistant HSV in hematopoietic stem cell recipients;<sup>20</sup> no specific data for HIV-infected individuals are available.

## **Special Considerations During Pregnancy**

Diagnosis of mucocutaneous HSV infections is the same for pregnant women as for non-pregnant women. Episodic therapy for first-episode HSV disease and for recurrences can be offered during pregnancy. Visceral disease is more likely to occur during pregnancy and can be fatal in rare cases. Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe (**AIII**).<sup>21</sup> The use of valacyclovir and famciclovir during pregnancy has been described and they appear to be safe and well tolerated.<sup>22</sup>

Valacyclovir use can be considered for treatment and suppressive therapy during pregnancy because of its simplified dosing schedule (**CIII**).

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate. The rate of HSV transmission to the newborn in HSV-2-seropositive pregnant women is low, except in those who acquire genital HSV late in pregnancy. The adverse sequelae for the fetus, however, can be very significant. The predominant risk for HSV transmission is maternal genital shedding of HSV at delivery. Cesarean delivery is recommended for women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor (**BII**).<sup>5</sup> Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes

outbreaks and reduces the need for cesarean delivery for recurrent HSV in HIV-seronegative women<sup>23</sup> and is likely to have similar efficacy in HIV-seropositive women. The effect of antiviral therapy late in pregnancy on the incidence of neonatal herpes is unknown. Suppressing therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks' gestation for pregnant women with recurrences of genital herpes during pregnancy **(BII)**.<sup>24</sup> There is no known benefit of suppressive therapy for women who are only seropositive for HSV-2 without a history of genital lesions. Maternal genital herpes was a risk factor for perinatal mother-to-child HIV transmission in the pre-highly active antiretroviral therapy era.<sup>25</sup> Whether HSV facilitates HIV transmission among pregnant women on HAART and whether HSV suppression reduces the risk for vertical HIV transmission during pregnancy, birth, or breastfeeding are unknown.

## Recommendations for Treating Herpes Simplex Virus (HSV) Infections

### Treating Orolabial Lesions (Duration: 5–10 days)

- Valacyclovir 1 g PO BID **(AIII)**, *or*
- Famciclovir 500 mg PO BID **(AIII)**, *or*
- Acyclovir 400 mg PO TID **(AIII)**

### Treating Initial or Recurrent Genital Lesions (Duration: 5–14 Days)

- Valacyclovir 1 g PO BID **(AI)**, *or*
- Famciclovir 500 mg PO BID **(AI)**, *or*
- Acyclovir 400 mg PO TID **(AI)**

### Treating Severe Mucocutaneous HSV Infections **(AIII)**

- Initial therapy acyclovir 5 mg/kg IV q8h
- After lesions begin to regress, change to oral therapy as above.
- Continue treatment until lesions have completely healed.

### Chronic Suppressive Therapy

#### *Indications:*

- For patients with severe recurrences **(AI)**, *or*
- Patients who want to minimize the frequency of recurrences **(AI)**

#### *Treatment:*

- Valacyclovir 500 mg PO BID **(AI)**, *or*
- Famciclovir 500 mg PO BID **(AI)**, *or*
- Acyclovir 400 mg PO BID **(AI)**
- Continue indefinitely without regard to CD4 count improvement.

### For Acyclovir-Resistant Mucocutaneous HSV infections

#### *Preferred Therapy:*

- Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response **(AI)**

#### *Alternative Therapy (Duration: 21–28 days or longer, based on clinical response) **(CIII)**:*

- Topical trifluridine, *or*
- Topical cidofovir, *or*
- Topical imiquimod, *or*
- IV cidofovir

#### **Note:**

- Topical formulations of trifluridine and cidofovir are not commercially available
- Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir

**Key to Acronyms:** BID = twice daily; HSV = herpes simplex virus; IV = intravenously; PO = orally; q(n)h = every "n" hours; TID = three times daily

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## Varicella-Zoster Virus Diseases (Last updated May 7, 2013; last reviewed May 7, 2013)

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### Epidemiology

More than 95% of adults (aged >20 years) born in the United States have immunity to varicella, the vast majority due to primary VZV infection, known as varicella (or chickenpox). Reactivation of latent VZV results in herpes zoster (or shingles). A person's lifetime risk for herpes zoster is 15% to 20%, with the highest incidence occurring in the elderly and immunocompromised individuals. The incidence of herpes zoster is >15-fold higher for HIV-infected adults than for age-matched controls.<sup>1</sup> Herpes zoster can occur in HIV-infected adults at any CD4 T lymphocyte (CD4) cell count, but frequency of disease is highest with CD4 counts of <200 cells/ $\mu$ L.<sup>2-4</sup> Antiretroviral therapy (ART) has not been shown to reduce the incidence of herpes zoster in adult populations: in fact, rates appear to be higher in the period immediately after initiation of ART. Lower frequency of herpes zoster in pediatric patients treated with ART has been observed, but it is difficult to separate ART effect from the impact of varicella vaccine.<sup>5,6</sup>

### Clinical Manifestations

Varicella rash tends to have a central distribution with lesions first appearing on the head, then trunk, and finally the extremities, evolving through stages of macules, papules, vesicles, pustules, and crusts. The rash is characterized by rapid evolution of lesions during the initial 8 to 12 hours and by successive crops of new lesions and by the presence of lesions in different stages of development at the same time. New vesicle formation continues for 2 to 4 days, accompanied by pruritis, fever, headache, malaise, and anorexia.<sup>7</sup> Primary varicella can cause substantial morbidity in HIV-seropositive adolescents and adults. Visceral dissemination, especially VZV pneumonitis, is well documented.<sup>7</sup> Because most HIV-infected adults in the United States are VZV seropositive, primary varicella is an uncommon occurrence in this population.

Herpes zoster manifests as a painful cutaneous eruption in a dermatomal distribution, often preceded by prodromal pain. The most common sites for herpes zoster are the thoracic dermatomes (40%–50% of cases), followed by cranial nerve (20%–25%), cervical (15%–20%), lumbar (15%), and sacral (5%) dermatomes. Skin changes begin with an erythematous maculopapular rash, followed by the appearance of clear vesicles and accompanied by pain (which may be severe). New vesicle formation typically continues for 3 to 5 days, followed by lesion pustulation and scabbing. Crusts typically persist for 2 to 3 weeks. About 20% to 30% of HIV-infected patients have one or more subsequent episodes of herpes zoster, which may involve the same or different dermatomes. The probability of a recurrence of herpes zoster within 1 year of the index episode is approximately 10%.<sup>3,8</sup> Approximately 10% to 15% of HIV-seropositive patients report post-herpetic neuralgia as a complication following herpes zoster.<sup>3,9</sup>

Most herpes zoster-related complications in HIV-seropositive patients, including disseminated herpes zoster, occur in patients with CD4 counts of <200 cells/ $\mu$ L.<sup>10</sup> The CNS is the primary target organ for herpes zoster dissemination in patients coinfecting with HIV. Various VZV-related neurologic syndromes occur in HIV-infected patients, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) are variants of necrotizing retinopathy caused by VZV. Although ARN can occur in both immunocompetent and immunocompromised patients, PORN occurs almost exclusively in AIDS patients with CD4 counts <100 cells/ $\mu$ L.<sup>11</sup> In contrast to ARN, PORN is characterized by minimal inflammation in the aqueous and vitreous humor, absence of retinal vasculitis, and multiple discrete peripheral lesions in the outer retinal layer.<sup>12</sup> PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.<sup>13</sup> Both ARN and PORN are associated with high rates of visual loss.

## Diagnosis

Varicella and herpes zoster are distinctive in appearance and diagnosis can usually be made clinically. Varicella can also be diagnosed retrospectively by documenting seroconversion. Immunocompromised persons can have atypical presentations and varicella may be difficult to distinguish from disseminated herpes zoster (as opposed to dermatomal herpes zoster); history of varicella or VZV exposure, a rash that began with a dermatomal pattern, and VZV testing to assess prior VZV infection may be helpful. When lesions are atypical or the diagnosis of VZV from other exanthems is uncertain, swabs from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or polymerase chain reaction (PCR). Additionally, scabs are very good specimens for PCR testing. PCR of lesions is the most sensitive and specific method for diagnosis of VZV infections. Histopathology and PCR (of blood or fluids such as cerebrospinal fluid or vitreous humor) can aid with diagnosis of VZV infections of visceral organs (e.g., pneumonitis, encephalitis, retinitis).<sup>14</sup> Routine serologic testing to determine the VZV serologic status of HIV-infected adults is not recommended.

## Preventing Exposure

HIV-infected persons who are susceptible to VZV (i.e., persons who have no history of varicella or shingles, who are seronegative for VZV, and who have no history of vaccination against VZV) should avoid exposure to individuals with varicella or herpes zoster (**AII**).

If household contacts of HIV-infected persons without evidence of immunity to varicella are themselves without evidence of immunity, then these household contacts should be vaccinated to prevent acquisition of varicella and potential transmission of wild-type VZV to their susceptible HIV-infected contacts (**BIII**).

## Preventing Disease

Long-term prophylaxis with antiviral drugs to prevent varicella **is not recommended** (**AIII**). Rather, for HIV-infected persons who are susceptible to VZV, post-exposure prophylaxis following known or suspected VZV exposure is recommended.

### *Vaccination To Prevent Primary Infection*

The live attenuated varicella vaccine has been documented to be safe and immunogenic in HIV-infected children with relatively preserved immune systems (CD4 lymphocyte percentage  $\geq 15\%$ )<sup>15-18</sup> and is recommended for them (**AI**)<sup>19</sup>. Varicella vaccination of HIV-seropositive children also reduces the risk of subsequent herpes zoster.<sup>6,18</sup> No studies have evaluated the vaccine in HIV-infected adolescents or adults, but varicella vaccination (2 doses, administered 3 months apart) may be considered in HIV-seropositive/VZV-seronegative persons  $\geq 8$  years old with CD4 counts  $\geq 200$  cells/ $\mu$ L (**CIII**).<sup>20</sup> If vaccination results in disease caused by vaccine virus (a rare event), therapy with acyclovir is recommended (**AIII**). Administration of varicella vaccine to more severely immunocompromised HIV-infected patients (CD4 counts  $< 200$  cells/ $\mu$ L) **is not recommended** (**AIII**). Because of the high prevalence of VZV seropositivity in adults, use of varicella vaccine in this population will be infrequent. If post-exposure VariZIG has been administered, an interval of at least 5 months is recommended before varicella vaccination (**CIII**).<sup>21</sup> If post-exposure acyclovir has been administered, an interval of at least 3 days is recommended before varicella vaccination (**CIII**).

### *Post-Exposure Prophylaxis To Prevent Primary Infection*

After close contact with a person who has active varicella or herpes zoster, HIV-infected adolescents and adults who are susceptible to VZV should receive varicella-zoster immune globulin (VariZIG<sup>TM</sup>) as soon as possible, but within 10 days after exposure (**AIII**).<sup>22</sup> Risk for VZV transmission is higher following exposure to a person with varicella than after exposure to localized herpes zoster. In the United States, VariZIG can be obtained only under a treatment investigational new drugs application (IND) by contacting FFF Enterprises (Temecula, CA), at (800) 843-7477. The duration of protection is at least 3 weeks. Patients receiving

monthly high-dose intravenous immune globulin (IVIG >400 mg/kg) are likely to be protected and probably do not require VariZIG if the last dose of IVIG was administered <3 weeks before exposure. Short-term post-exposure administration of acyclovir or valacyclovir beginning 7 to 10 days after exposure<sup>23</sup> may be considered for preventing varicella among susceptible HIV-infected adolescents or adults but this intervention has not been studied in these populations (**BIII**). Among VZV-susceptible immunocompetent children, post-exposure varicella vaccination has been shown to reduce the risk for varicella and is more effective than pre-emptive therapy with antiviral drugs; however the efficacy of post exposure varicella vaccination for adolescents and adults has also not been established.

## Treating Disease

### Varicella

No controlled prospective studies of antiviral therapy for varicella in HIV-infected adults have been reported. For uncomplicated varicella, the preferred treatment options are valacyclovir (1 g PO 3 times daily), or famciclovir (500 mg PO 3 times daily) for 5 to 7 days (**AII**). Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg 5 times daily) can be an alternative option (**BII**), Intravenous (IV) acyclovir for 7 to 10 days is the recommended initial treatment for HIV-infected patients with severe varicella (**AIII**).<sup>7,24,25</sup> If no evidence of visceral involvement with VZV is apparent, switching to oral antiviral therapy after the patient has defervesced may be permissible (**BIII**).<sup>26</sup>

### Herpes zoster

Prompt antiviral therapy should be instituted in all HIV-seropositive patients whose herpes zoster is diagnosed within 1 week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in HIV-infected patients are oral valacyclovir (**AII**), famciclovir (**AII**), or acyclovir (**BII**) (doses as above) for 7 to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. If cutaneous lesions are extensive or if visceral involvement is suspected, IV acyclovir should be initiated and continued until clinical improvement is evident (**AII**).<sup>27</sup> A switch from IV acyclovir to oral antiviral therapy (to complete a 10- to 14-day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral VZV infection are improving (**BIII**). Because of the absence of data to support benefit in this population, adjunctive corticosteroid therapy for herpes zoster **is not recommended** (**AIII**). Optimization of ART is recommended for all patients with VZV infections that are difficult to treat (e.g., retinitis, encephalitis) (**AIII**).

Optimal antiviral therapy for PORN remains undefined.<sup>28</sup> The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. Treatment should include IV and intravitreal antiviral therapy directed at VZV plus effective ART (**AIII**).<sup>29</sup> Treatment regimens for PORN recommended by certain specialists include:

- a) a combination of IV ganciclovir and foscarnet, plus intravitreal injections of ganciclovir and/or foscarnet,  
*or*
- b) IV acyclovir, intravitreal foscarnet, plus ganciclovir ocular implant.

Optimization of ART in HIV-infected patients with PORN is also recommended (**AIII**). Anecdotal reports have described success with IV cidofovir. Intravitreal cidofovir should not be used because such injections may be associated with loss of intraocular pressure. ARN appears to be more responsive to antiviral therapy; one recommended treatment is high-dose IV acyclovir (10 mg/kg every 8 hours for 10–14 days), followed by prolonged oral valacyclovir (1 gram 3 times daily for 6 weeks) (**AIII**). Involvement of an experienced ophthalmologist in management of patients with VZV retinitis is strongly recommended (**AIII**).

## ***When to Start ART***

A single uncomplicated episode of herpes zoster in an HIV-infected individual is not an indication to initiate ART nor is it an indication to defer ART. Initiation of ART should be strongly considered in a patient who has multiple recurrences of herpes zoster or who has a complication of VZV disease (e.g., PORN, encephalitis) (**AIII**).

## ***Monitoring of Response to Therapy and Adverse Events (Including IRIS)***

For monitoring and adverse event recommendations related to anti-herpesvirus drugs, see preceding sections on herpes simplex virus and cytomegalovirus.

Immune reconstitution following initiation of ART appears to be associated with an increased frequency of VZV reactivation.<sup>30-33</sup> Observational studies have shown the risk of zoster to increase 2- to 4-fold between 4 and 16 weeks after initiating ART. The clinical presentation and natural history of herpes zoster in the setting of immune reconstitution do not differ from those observed in other HIV-infected patients and such episodes should be managed in the same manner.

## ***Managing Treatment Failure***

Treatment failure caused by resistance of VZV to acyclovir (and related drugs) are rare and should be suspected if lesions do not improve within 10 days of initiation of therapy or if they have an atypical (e.g., verrucous) appearance. A viral culture should be obtained, and if VZV is isolated, susceptibility testing performed to establish antiviral drug susceptibility or resistance and to document the need for alternative therapy. Among patients with suspected or proven acyclovir-resistant VZV infections, treatment with IV foscarnet is recommended (**AII**).<sup>34</sup> IV cidofovir is a potential alternative (**AIII**).

## **Preventing Recurrence**

The efficacy of long-term antiviral prophylaxis to prevent herpes zoster recurrences in HIV-seropositive persons has not been evaluated and is not routinely recommended.

An attenuated virus vaccine for prevention of herpes zoster is FDA-approved for use in immunocompetent persons aged  $\geq 50$  years, but is recommended for use beginning at age 60 years by the Advisory Committee on Immunization Practices (ACIP). The zoster vaccine is contraindicated in persons with CD4 cell counts  $< 200$  cells/ $\mu$ L.

## **Special Considerations During Pregnancy**

HIV-infected pregnant women who are susceptible to VZV and are in close contact with a person with active varicella or herpes zoster should receive VariZIG as soon as possible (within 10 days)<sup>22</sup> after exposure to VZV (**AIII**). If oral acyclovir is used for post-exposure prophylaxis, VZV serology should be performed so that the drug can be discontinued if the patient is seropositive for VZV (**CIII**). Pregnant women should not receive varicella vaccine (**AIII**).

Specific risks among HIV-infected women with varicella during pregnancy have not been reported. For HIV-seronegative women with varicella, the risk of transmitting VZV to the infant resulting in congenital varicella syndrome is 0.4% when infection occurs at or before 12 weeks' gestation, 2.2% with infection at 13 to 20 weeks, and is negligible after 20 weeks.<sup>35</sup> Women with varicella during the first half of pregnancy should be counseled about the risks and offered detailed ultrasound surveillance for findings indicative of fetal congenital varicella syndrome.<sup>35</sup> Administration of varicella-zoster immune globulin is recommended primarily to prevent complications in the mother; whether it has any benefit in prevention of congenital varicella syndrome is unknown. Infants born to women who have varicella from 5 days before until 2 days after delivery should receive VariZIG to reduce the severity and mortality of neonatal varicella acquired by exposure to maternal viremia (**AIII**).

Oral acyclovir or valacyclovir are the preferred treatments for HIV-infected pregnant women who have uncomplicated varicella during pregnancy (**BIII**). Pregnant women who have severe varicella or who exhibit signs or symptoms of VZV pneumonitis should be hospitalized and treated with IV acyclovir (10 mg/kg every 8 hours) (**AII**).

No controlled studies of antiviral therapy of herpes zoster during pregnancy have been reported. Recommended therapy for uncomplicated shingles in pregnant HIV-infected women is oral acyclovir or

## Recommendations for Preventing and Treating Varicella Zoster Virus (VZV) Infections (page 1 of 2)

### Pre-Exposure Prevention Of VZV Primary Infection

#### *Indications:*

- Adult and adolescent patients with CD4 count  $\geq 200$  cells/mm<sup>3</sup> without documentation of vaccination, health-care provider diagnosis or verification of a history of varicella or herpes zoster, laboratory confirmation of disease, or persons who are seronegative for VZV (**CIII**)

**Note:** Routine VZV serologic testing in HIV-infected adults and adolescents is not recommended.

#### *Vaccination:*

- Primary varicella vaccination (Varivax™), 2 doses (0.5 mL SQ) administered 3 months apart (**CIII**)
- If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended (**AIII**).
- VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts (**BIII**).
- If post-exposure VariZIG has been administered, wait at least 5 months before varicella vaccination (**CIII**)
- If post-exposure acyclovir has been administered, wait at least 3 days before varicella vaccine (**CIII**)

### Post-Exposure Prophylaxis:

#### *Indication (AIII):*

- Close contact with a person who has active varicella or herpes zoster, *and*
- Is susceptible to VZV (i.e., has no history of vaccination or of either condition, or is known to be VZV seronegative)

#### *Preferred Prophylaxis:*

- VariZIG™ 125 IU per 10 kg (maximum of 625 IU) IM, administered as soon as possible and within 10 days after exposure to a person with active varicella or herpes zoster (**AIII**)
- VariZIG can be obtained only through an expanded access program under a treatment IND by contacting FFF Enterprise at (800) 843-7477
- If post-exposure VariZIG has been administered, wait at least 5 months before varicella vaccination (**CIII**)

**Note:** Patients receiving monthly high dose IVIG (i.e., > 400 mg/kg) are likely to be protected against VZV and probably do not require VariZIG if the last dose of IVIG was administered <3 weeks before VZV exposure

#### *Alternative Prophylaxis (Begin 7–10 Days After Exposure):*

- Acyclovir 800 mg PO 5 times/day for 5–7 days (**BIII**), *or*
- Valacyclovir 1 g PO TID for 5–7 days (**BIII**)

#### **Note:**

- Neither these pre-emptive interventions nor post-exposure varicella vaccination have been studied in HIV-infected adults and adolescents
- If acyclovir or valacyclovir is used, varicella vaccines should not be given until at least 72 hours after the last dose of the antiviral drug.

### **Treatment of Varicella Infections**

#### Primary Varicella Infection (Chickenpox)

##### Uncomplicated Cases

###### *Preferred Therapy:*

- Valacyclovir 1 g PO TID **(AII)**, or
- Famciclovir 500 mg PO TID **(AII)**

###### *Alternative Therapy:*

- Acyclovir 800 mg PO 5 times daily **(BII)**

###### *Duration:*

- 5–7 days

##### Severe or Complicated Cases:

- Acyclovir 10–15 mg/kg IV q8h for 7–10 days **(AIII)**
- May switch to oral famciclovir, valacyclovir, or acyclovir after defervescence if no evidence of visceral involvement is evident **(BIII)**

#### Herpes Zoster (Shingles)

##### Acute Localized Dermatomal

###### *Preferred Therapy*

- Valacyclovir 1000 mg PO TID **(AII)**, or
- Famciclovir 500 mg PO TID **(AII)**

###### *Alternative Therapy*

- Acyclovir 800 mg PO 5 times daily **(BII)**

###### *Duration*

- 7–10 days, longer duration should be considered if lesions resolve slowly

##### Extensive Cutaneous Lesion or Visceral Involvement

- Acyclovir 10–15 mg/kg IV q8h until clinical improvement is evident **(AII)**
- Switch to oral therapy (valacyclovir 1 g TID, famciclovir 500 mg TID, or acyclovir 800 mg PO 5 times daily)—to complete a 10–14 day course, when formation of new lesions has ceased and signs and symptoms of visceral VZV infection are improving **(BIII)**

#### PORN

- (Ganciclovir 5 mg/kg + foscarnet 90 mg/kg) IV q12h plus (ganciclovir 2 mg/0.05mL +/- foscarnet 1.2 mg/0.05mL) intravitreal twice weekly **(AIII)**, or
- Acyclovir 10–15 mg/kg IV q8h + ganciclovir ocular implant + intravitreal foscarnet **(AIII)**
- Optimize ART regimen **(AIII)**
- Involvement of an experienced ophthalmologist is strongly recommended **(AIII)**
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic response in consultation with ophthalmologist.

#### ARN

- Acyclovir 10 mg/kg IV q8h for 10–14 days, followed by valacyclovir 1 g PO TID for 6 weeks **(AIII)**
- Involvement of an experienced ophthalmologist is strongly recommended **(AIII)**
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic response in consultation with ophthalmologist.

**Key to Acronyms:** ARN = acute retinal necrosis; CD4 = CD4 T lymphocyte cell; IND = investigational new drug application; IU = international units; IV = intravenously; IVIG = intravenous immunoglobulin; PO = orally; PORN = progressive outer retinal necrosis; q(n)h = every “n” hours; SQ = subcutaneously; TID = three times a day; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus

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# Human Herpesvirus-8 Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

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## Epidemiology

Human herpesvirus-8 (HHV-8) seroprevalence among the general population in the United States is 1% to 5%. The seroprevalence is greater among men who have sex with men (20%–77%),<sup>1</sup> regardless of HIV infection, and is also higher in certain Mediterranean countries (10%–20%) and in parts of sub-Saharan Africa (30%–80%).<sup>2</sup> HHV-8 is etiologically associated with all forms of Kaposi's sarcoma ([KS] i.e., classic, endemic, transplant-related, and AIDS-related) and certain rare neoplastic disorders (such as primary effusion lymphoma) and lymphoproliferative disorders (multicentric Castleman's disease) The precise pathogenesis is unclear even though seroconversion to HHV-8 precedes the development of these tumors.<sup>3</sup> Patients who are HHV-8 seropositive and have HHV-8 viremia have an increased risk (approximately nine-fold) for developing KS compared with HHV-8 seropositive men without HHV-8 viremia.<sup>4</sup> HHV-8 viremia almost always accompanies symptomatic episodes of multicentric Castleman's disease.<sup>5</sup>

The overall prevalence of KS was as high as 30% among patients with AIDS before the advent of effective antiretroviral therapy (ART).<sup>6</sup> The incidence of KS, which increased nearly 10-fold in the United States between 1981 and 1987, began to gradually decline in 1987.<sup>7</sup> Reasons for this reduction in KS incidence prior to the widespread availability of ART are likely to be multiple, including the deaths of patients with advanced AIDS who were most susceptible to KS, and the increasing use by HIV-infected individuals of antiviral drugs that may have activity against HHV-8 (zidovudine for the treatment of HIV; ganciclovir, foscarnet, and cidofovir use for treatment of CMV disease).<sup>8</sup> Supporting the latter hypothesis, observational studies indicate that patients receiving ganciclovir or foscarnet (but not acyclovir) develop KS at a reduced rate.<sup>9–12</sup> A more marked reduction in KS incidence occurred in 1996, shortly after the introduction of protease inhibitor-containing ART in the United States. Today the incidence of KS in the United States remains approximately 3-fold higher than before the HIV pandemic, and notably KS incidence has not declined in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.<sup>13</sup> Primary effusion cell lymphoma and multicentric Castleman's disease remain rare.<sup>14</sup>

KS and primary effusion lymphoma are described most frequently among HIV-infected persons with more advanced immunosuppression (CD4 T lymphocyte [CD4] cell counts <200 cells/ $\mu$ L), although they can occur at any CD4 cell count. Multicentric Castleman's disease can present at any CD4 cell count. Recent reports of KS occurring at higher CD4 cell counts in the United States<sup>15,16</sup> suggest that clinicians caring for patients with HIV should be vigilant for the clinical manifestations of KS in patients at risk of HHV-8 infection, regardless of CD4 cell count.

## Clinical Manifestations

Most individuals with chronic HHV-8 infection are asymptomatic.<sup>17</sup> Acquisition of HHV-8 in immunocompetent children and organ transplant recipients has been associated with a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS.<sup>18,19</sup> KS manifestations vary widely, but most patients have nontender, purplish, indurated skin lesions. Intraoral lesions are common and visceral dissemination can occur, occasionally without the presence of skin lesions. Multicentric Castleman's disease manifests with generalized adenopathy and fever and can progress to multi-organ failure.<sup>14</sup> Primary effusion lymphoma characteristically presents with effusions of the pleural, pericardial, or abdominal spaces; mass lesions can be seen but are less common manifestations.

## Diagnosis

The diagnoses of KS, multicentric Castleman's disease and primary effusion lymphoma depend on cytologic and immunologic cell markers, as well as histology. Routine screening for HHV-8 by polymerase chain

reaction (PCR) or serologic testing for HHV-8 antibody is not indicated for HIV-infected persons. Use of PCR to quantify HHV-8 in the peripheral blood has no established role in the diagnosis of KS, multicentric Castleman's disease and primary effusion lymphoma.<sup>5</sup>

## Preventing Exposure

Asymptomatic HHV-8 infection is often associated with HHV-8 shedding in the saliva and occasional shedding in genital secretions.<sup>1,17,20</sup> Viral shedding may result in HHV-8 transmission to uninfected partners through behaviors associated with exposure to saliva or genital secretions. Recommendations related to preventing exposure to HHV-8 do not exist; screening patients for HHV-8 serostatus and recommending behavioral modifications based on such information is not likely to be highly effective, has not been validated, and **is not currently recommended (CIII)**.

## Preventing Disease

Despite observational evidence supporting a role for anti-HHV-8 therapy in preventing the development of KS, the toxicity of current anti-HHV-8 therapy outweighs the potential benefits of administration **(BIII)**. Because the strongest risk factor for the development of KS in HIV-positive individuals is a low CD4 cell count,<sup>21</sup> early initiation of ART is likely to be the most effective measure for the prevention of KS.

## Treating Disease

Although ganciclovir, foscarnet, and cidofovir have *in vitro* activity against HHV-8 and limited studies indicate these agents may be associated with reduced KS disease progression or lesion regression, larger and more definitive studies are needed to determine whether antiviral therapy has a useful role in managing HHV-8-associated diseases. KS regression has been documented after ganciclovir or foscarnet therapy, although one study indicated cidofovir was ineffective.<sup>22</sup>

The use of IV ganciclovir or oral valganciclovir is an option for treatment of multicentric Castleman's disease **(CII)**. A 3-week course of twice-daily IV ganciclovir or oral valganciclovir was associated with remissions in multicentric Castleman's disease in one report,<sup>23</sup> and a combination of valganciclovir and high-dose zidovudine given for 7 to 21 days led to durable clinical remissions of the disease **(CII)**.<sup>24</sup> Rituximab also is an effective alternative to antiviral therapy in the treatment of multicentric Castleman's disease **(CII)**,<sup>25,26</sup> though up to one-third of patients treated with rituximab may have subsequent exacerbations or emergence of KS.<sup>27,28</sup>

Chemotherapy, in combination with ART, should be administered to patients with primary effusion cell lymphoma or visceral KS **(AI)** and is likely to be a useful adjunctive therapy in individuals with widely disseminated cutaneous KS **(BIII)**. Some clinicians recommend valganciclovir as adjunctive therapy in the treatment of primary effusion lymphoma but there are no convincing data that it is useful **(CIII)**.<sup>29,30</sup>

Detailed recommendations for treatment of HHV-8 malignancies (including chemotherapy and radiation therapy) are beyond the scope of these guidelines. Treatment should be undertaken in consultation with an experienced specialist **(AIII)**.

### ***Special Considerations When Starting ART***

Early initiation of ART is likely to prevent incident KS and primary effusion cell lymphoma, though no studies have confirmed this hypothesis to date. ART that suppresses HIV replication should be administered to all HIV-infected patients with KS, primary effusion cell lymphoma, or multicentric Castleman's disease **(AII)**, although insufficient evidence exists to support using one ART regimen over another.

### ***Monitoring of Response to Therapy and Adverse Events (Including IRIS)***

Immune reconstitution inflammatory syndrome (IRIS) has been a reported complication among HHV-8-

infected patients initiating ART.

**KS:** In one series, new onset KS or exacerbations of previously stable disease were the most common IRIS syndrome in a cohort of HIV-infected patients in Seattle.<sup>31</sup> Over half of Ugandan patients with mild-to-moderate KS experienced an exacerbation when initiating ART.<sup>32</sup> Reliable predictors of KS-IRIS have not been identified.

**Multicentric Castleman's disease:** A small number of patients with HIV-associated multicentric Castleman's disease were also observed to have a clinical decompensation upon initiation of ART.<sup>33,34</sup>

**Primary effusion lymphoma:** No data exist on the frequency with which initiation of ART complicates the course of primary effusion lymphoma.

Taken together, it is clear that neither the incidence nor predictors of HHV-8-associated IRIS are well-described, but suppression of HIV replication and immune reconstitution are key components of therapy and initiation of ART should not be delayed (**AIII**).

## Preventing Recurrence

Effective suppression of HIV replication with ART in HIV-infected patients with KS may prevent KS progression or occurrence of new lesions, and because KS is an AIDS-defining cancer, ART is indicated for all patients with active KS (**AII**). Suppression of HIV replication also is recommended for patients with multicentric Castleman's disease (**AIII**) and those with malignant lymphoproliferative disorders (**AIII**).

## Special Considerations During Pregnancy

The seroprevalence of HHV-8 infection among HIV-infected pregnant women varies by geographic area, ranging from 1.7% among U.S.-born and 3.6% among Haitian-born women in New York City to 11.6% among pregnant women from 4 other U.S. cities.<sup>35</sup> Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels,<sup>36</sup> although levels of HHV-8 DNA in the peripheral blood may increase late in pregnancy.<sup>37</sup> HHV-8 seropositivity does not appear to influence pregnancy outcome. Routine screening for HHV-8 by PCR or serology is not indicated for HIV-infected pregnant women (**AIII**). Antiviral therapy for HHV-8 infection in pregnancy **is not recommended** (**AIII**).

*In vitro* models suggest that beta-human chorionic gonadotropin induces regression of KS tumors, but clinical reports on the incidence and natural history of KS in pregnancy are conflicting.<sup>38-41</sup>

Perinatal transmission of HHV-8 occurs infrequently. Evidence supporting vertical transmission during pregnancy or the intrapartum period includes cases of KS occurring in the infant shortly after birth,<sup>42,43</sup> higher risk for transmission with higher maternal antibody titer (and, by inference, higher maternal levels of HHV-8),<sup>44</sup> and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants.<sup>45</sup> Data indicate increased mortality through age 24 months among HIV-infected infants born to HHV-8-seropositive compared with HHV-8-seronegative mothers,<sup>42-44,46-51</sup> but these studies could not completely account for other confounding factors affecting HIV-infected infants. The majority of studies document a substantially higher rate of HHV-8 seropositivity among children born to HHV-8 antibody-positive compared with HHV-8 antibody-negative women.<sup>46-51</sup>

## Recommendations for Treating HHV-8 Diseases—Kaposi Sarcoma (KS), Primary Effusion Lymphoma (PEL), Multicentric Castleman’s Disease (MCD)

### **Mild-to-Moderate KS:**

- Initiation or optimization of ART (**AII**)

### **Advanced KS:**

- Chemotherapy (in consultation with specialist) + ART [visceral KS (**AI**) or widely disseminated KS (**BIII**)]

### **PEL:**

- Chemotherapy (in consultation with specialist) + ART (**AI**)
- Oral valganciclovir or IV ganciclovir might be used as adjunctive therapy (**CIII**)

### **MCD:**

*Preferred Therapy (in consultation with a specialist):*

- Valganciclovir 900 mg PO BID (**CII**) for 3 weeks, *or*
- Ganciclovir 5 mg/kg IV q12h (**CII**) for 3 weeks, *or*
- Valganciclovir 900 mg PO BID + zidovudine 600 mg PO q6h for 7–21 days (**CII**)

*Alternative Therapy for MCD:*

- Rituximab 375 mg/m<sup>2</sup> given weekly for 4–8 weeks, may be an alternative to, or used adjunctively with, antiviral therapy (**CII**)

### **Other Considerations:**

- Patients who received rituximab for treatment of MCD may experience subsequent exacerbation or emergence of KS

**Key to Acronyms:** ART = antiretroviral therapy; BID = twice daily; IV = intravenously; KS = Kaposi Sarcoma; MCD = multicentric Castleman’s disease; PEL = primary effusion lymphoma; PO = orally; q(n)h = every “n” hours

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