



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

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Varicella-Zoster Virus Diseases (Last updated July 8, 2013; last reviewed July 8, 2013)

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.¹ 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/ μ L.²⁻⁴ 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.^{5,6}

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 pruritus, fever, headache, malaise, and anorexia.⁷ Primary varicella can cause substantial morbidity in HIV-seropositive adolescents and adults. Visceral dissemination, especially VZV pneumonitis, is well documented.⁷ 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%.^{3,8} Approximately 10% to 15% of HIV-seropositive patients report post-herpetic neuralgia as a complication following herpes zoster.^{3,9}

Most herpes zoster-related complications in HIV-seropositive patients, including disseminated herpes zoster, occur in patients with CD4 counts of <200 cells/ μ L.¹⁰ 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/ μ L.¹¹ 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.¹² PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.¹³ 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 serologic 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).¹⁴ 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 $\geq 15\%$)¹⁵⁻¹⁸ and is recommended for them (**AI**).¹⁹ Varicella vaccination of HIV-seropositive children also reduces the risk of subsequent herpes zoster.^{6,18} 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 ≥ 8 years old with CD4 counts ≥ 200 cells/ μL (**CIII**).²⁰ 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/ μL) 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 varicella-zoster immune globulin (VariZIGTM) has been administered, an interval of at least 5 months is recommended before varicella vaccination (**CIII**).²¹ 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 VariZIG as soon as possible, but within 10 days after exposure (**AIII**).²² 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 exposure²³ 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 (**BII**). Intravenous (IV) acyclovir for 7 to 10 days is the recommended initial treatment for HIV-infected patients with severe varicella (**AIII**).^{7,24,25} If no evidence of visceral involvement with VZV is apparent, switching to oral antiviral therapy after the patient has defervesced may be permissible (**BIII**).²⁶

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**).²⁷ 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.²⁸⁻³⁰ Outcomes with intravenous acyclovir or ganciclovir monotherapy were poor. Better results were obtained with intravenous ganciclovir (or the combination of ganciclovir plus foscarnet), along with intravitreal antiviral drug injections.²⁹ Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet) (**AIII**).^{31,32} Treatment regimens for PORN recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet *plus* intravitreal injections of ganciclovir and/or foscarnet (**AIII**). The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy.

Optimization of ART in HIV-infected patients with PORN is also recommended (**AIII**).³² Anecdotal reports have described success with IV cidofovir for PORN. Intravitreal cidofovir should not be used because such injections may be associated with loss of intraocular pressure and other adverse effects. Ganciclovir ocular implants, previously recommended by some experts, are no longer manufactured.

ARN appears to be more responsive than PORN to antiviral therapy. One recommended treatment is high-dose IV acyclovir (10–15 mg/kg every 8 hours for 10–14 days), followed by prolonged oral valacyclovir (1 gram 3 times daily for 6 weeks) (**AIII**). Many experts would also include 1 or 2 doses of intravitreal ganciclovir as part of the initial induction therapy (**BIII**). 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.³³⁻³⁶ 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) is rare, but should be suspected if clinical findings do not improve within 10 days of initiation of therapy or if skin lesions 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**).³⁷ 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 ≥ 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/ μ 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)²² 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.³⁸ 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.³⁸ 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 valacyclovir (**BIII**). Pregnant women should not receive the herpes zoster vaccine (**AIII**).

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 ≥ 200 cells/mm³ 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 international units per 10 kg (maximum of 625 international units) 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

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

Note: ganciclovir ocular implants are no longer commercially available

ARN

- Acyclovir 10 - 15 mg/kg IV q8h for 10–14 days, followed by valacyclovir 1 g PO TID for 6 weeks PLUS ganciclovir 2 mg/0.05mL intravitreal twice weekly X 1-2 doses **(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 responses in consultation with ophthalmologist.

Key to Acronyms: ARN = acute retinal necrosis; CD4 = CD4 T lymphocyte cell; IND = investigational new drug application; 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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