

# Varicella-Zoster Virus Diseases

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## Epidemiology

More than 95% of adults (aged >20 years) born in the United States have immunity to varicella-zoster virus (VZV), mostly due to primary VZV infection, known as varicella (or chickenpox).<sup>1</sup> A varicella vaccine became available in the United States in 1995; most children born in the United States after 2005 are immune to varicella as a result of vaccination.<sup>2</sup> Reactivation of latent VZV results in herpes zoster (shingles). In the general population, the incidence of herpes zoster is about 3.6 cases per 1,000 person-years, with much higher incidence seen among elderly and immunocompromised individuals. Before the availability of antiretroviral therapy (ART), the incidence of herpes zoster was more than 15-fold higher among adults with HIV than among age-matched controls without HIV.<sup>3,4</sup> Herpes zoster can occur in adults with HIV at any CD4 T lymphocyte (CD4) cell count, but with CD4 counts <200 cells/mm<sup>3</sup>, the risk of disease is higher.<sup>5-8</sup> In addition, HIV viremia is associated with an increased risk for incident herpes zoster.<sup>9</sup> ART has been shown to reduce the incidence of herpes zoster in adults with HIV, presumably because of immune restoration, although the risk of herpes zoster remains threefold higher in adults with HIV than in the general population.<sup>7,10-13</sup> Several studies have demonstrated that the risk of herpes zoster in adults with HIV is increased in the 6-month period immediately after initiation of ART, possibly because of an immune reconstitution inflammatory syndrome (IRIS)-related mechanism.<sup>7,10,13,14</sup>

## Clinical Manifestations

Varicella rash tends to have a central distribution, with lesions first appearing on the head, then the 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 after onset, by successive crops of new lesions, and by the presence of lesions in different stages of development. New vesicle formation continues for 2 to 4 days, accompanied by pruritus, fever, headache, malaise, and anorexia.<sup>15</sup> Primary varicella can cause substantial morbidity in adolescents and adults with HIV. Visceral dissemination, especially VZV pneumonitis, is well documented.<sup>15</sup> Because most adults with HIV 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% to 50% of cases), followed by cranial nerve (20% to 25%), cervical (15% to 20%), lumbar (15%), and sacral (5%) dermatomes.<sup>16</sup> 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 people with HIV 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>5,17</sup> Approximately 10% to 15% of people with HIV report post-herpetic neuralgia as a complication following herpes zoster.<sup>5,18</sup>

When herpes zoster involves the nasociliary branch of the trigeminal nerve, the eye can be affected (herpes zoster ophthalmicus [HZO]), resulting in keratitis (inflammation of the cornea) or anterior

uveitis (inflammation of the iris and anterior ciliary body) or both. Vesicles on the tip of the nose (Hutchinson sign) are a clue that the nasociliary branch is involved. With corneal involvement, there may be an initial brief period during which the corneal epithelium is infected with VZV, but the major problem is inflammation of the corneal stroma, which can result in scarring, neovascularization, or necrosis with loss of vision. Stromal keratitis can be chronic. Once it occurs, VZV-associated anterior uveitis also tends to be chronic and can result in increased intraocular pressure or glaucoma, scarring of intraocular tissues, and cataract.

Stromal keratitis and anterior uveitis may not develop immediately after the appearance of skin vesicles on the forehead and scalp; therefore, patients with normal eye examinations initially should receive follow-up eye examinations, even after the skin lesions heal. Antiviral treatment of herpes zoster at the onset of cutaneous lesions reduces the incidence and severity of ophthalmic involvement.

Some patients with HZO may develop late dendriform lesions of the corneal epithelium that contain virus and will respond rapidly to systemic or topical anti-herpetic medications. These lesions are usually painful. In one study, the median time from onset of HZO to development of late dendriform lesions was 5 months, and the risk of recurrences decreased over time.<sup>19</sup> The frequency with which these late infectious lesions occur has not been determined.

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<sup>22</sup> in patients with AIDS with CD4 counts  $<100$  cells/mm<sup>3</sup>. In contrast to ARN, PORN is characterized by minimal inflammation in the aqueous and vitreous humor, absence of occlusive retinal vasculitis, and multiple discrete peripheral lesions that manifest initially as yellow foci of retinal opacification in the outer retinal layers.<sup>23</sup> PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.<sup>24</sup> Both ARN and PORN are associated with high rates of loss of vision.

People with HIV who have CD4 counts  $<200$  cells/mm<sup>3</sup> are at highest risk of herpes zoster–related complications, including disseminated herpes zoster.<sup>20</sup> The central nervous system (CNS) is a target organ for herpes zoster dissemination in patients coinfecting with HIV. Various VZV-related neurologic syndromes occur in people with HIV, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.<sup>21</sup>

## Diagnosis

Varicella and herpes zoster are typically distinctive in appearance and usually can be diagnosed clinically. Varicella also can be diagnosed retrospectively by documenting seroconversion (i.e., immunoglobulin G [IgG] antibody negative to positive). In immunocompromised persons, varicella may be difficult to distinguish from disseminated herpes zoster (as opposed to dermatomal herpes zoster); a history of VZV exposure, a rash that began with a dermatomal pattern, and VZV serologic testing to assess prior VZV infection may be helpful to distinguish disseminated herpes zoster from varicella. When lesions are atypical or difficult to distinguish from those due to other potential etiologies (including herpes simplex virus [HSV]), swabs of vesicular fluid from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or polymerase chain reaction (PCR). Additionally, scabs may be adequate 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>25</sup>

## Preventing Exposure

People with HIV who are susceptible to VZV (i.e., people who have no history of chickenpox 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 (**CIII**).

Household contacts of people with HIV without evidence of immunity to VZV should be vaccinated to prevent acquisition of varicella and potential transmission of wild-type VZV to susceptible contacts with HIV (**BIII**).

## Preventing Disease

### *Vaccination to Prevent Primary Infection (Varicella)*

The live attenuated varicella vaccine (Varivax<sup>®</sup>) has been documented to be safe and immunogenic in children with HIV who have relatively preserved immune systems (CD4 percentage  $\geq 15\%$ )<sup>26-29</sup> and is recommended for this population of children with HIV.<sup>30</sup> Varicella vaccination of children with HIV also reduces the risk of subsequent herpes zoster.<sup>29,31</sup>

VZV-seronegative adults are potential candidates for varicella vaccination. Some experts would serologically screen adults with HIV without a history of prior varicella or varicella vaccination for VZV IgG. However, the value of this approach may be limited by the lack of sensitivity of commercially available VZV antibody assays (particularly for vaccine-induced antibody).<sup>32,33</sup> No studies have evaluated the vaccine in adolescents or adults with HIV, but many experts recommend varicella vaccination (2 doses, administered 3 months apart) for VZV-susceptible people with HIV aged  $\geq 8$  years with CD4 counts  $\geq 200$  cells/mm<sup>3</sup> (**BIII**).<sup>34</sup> If varicella 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 people with HIV (CD4 counts  $< 200$  cells/mm<sup>3</sup>) is **contraindicated** (**AIII**). Given the high prevalence of VZV seropositivity in adults, administration of varicella vaccine for adults will be infrequent.

If post-exposure varicella-zoster immune globulin (VariZIG<sup>™</sup>) has been administered, an interval of at least 5 months is recommended before varicella vaccination (**CIII**).<sup>35</sup> If post-exposure acyclovir has been administered, an interval of at least 3 days is recommended before varicella vaccination (**CIII**).

### *Pre-Exposure Prophylaxis to Prevent Primary Infection (Varicella)*

Long-term prophylaxis with anti-VZV drugs, such as acyclovir or valacyclovir, to prevent varicella **is not recommended** (**AIII**).

### *Post-Exposure Prophylaxis to Prevent Primary Infection (Varicella)*

For people with HIV who are susceptible to VZV, post-exposure prophylaxis following known or suspected VZV exposure is recommended (**AII**). After close contact with a person who has active varicella or herpes zoster, adolescents and adults with HIV who are susceptible to VZV (particularly those with CD4 counts  $< 200$  cells/mm<sup>3</sup>) should receive VariZIG as soon as possible (preferably

within 96 hours), but up to 10 days after exposure (**AIII**).<sup>36</sup> Given the cost of obtaining VariZIG, it is reasonable to check VZV serology before administering VariZIG to people who do not have a clinical history of chickenpox or shingles and no documentation of varicella vaccination (**AIII**). The risk of VZV transmission is greater with exposure to varicella than localized herpes zoster. In the United States, VariZIG is commercially available from a broad network of specialty distributors (listed at: [www.varizig.com](http://www.varizig.com)). The duration of protection from VariZIG is at least 3 weeks. Patients receiving monthly infusions of high-dose intravenous immune globulin (IVIG >400 mg/kg) are likely to be protected and probably do not require VariZIG if they received a dose of IVIG <3 weeks before VZV exposure. A 5- to 7-day course of post-exposure acyclovir or valacyclovir beginning 7 to 10 days after exposure is recommended by some experts to prevent varicella among VZV-susceptible adolescents or adults with HIV, but this intervention has not been studied in these populations (**BIII**).<sup>37</sup> 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 people with HIV has not been studied and **is not recommended**.

### ***Antiviral Prophylaxis to Prevent Re-Activation Disease (Herpes Zoster)***

Long-term administration of anti-VZV drugs to individuals with HIV to prevent episodes of herpes zoster is not routinely recommended (**AII**). However, in a randomized, placebo-controlled study in Africa that evaluated daily acyclovir prophylaxis (acyclovir 400 mg orally [PO] twice a day) administered to people with HIV/HSV-2 coinfection who were not taking ART, acyclovir prophylaxis reduced the rate of herpes zoster by 62%.<sup>38</sup> Acyclovir did not prevent recurrent zoster episodes in patients with prior history of herpes zoster.<sup>38</sup> People with HIV who are taking suppressive anti-herpes medications (i.e., acyclovir, valacyclovir, or famciclovir) for other indications—such as prevention of genital herpes—may receive some additional benefit in reduction of risk of herpes zoster, but the relative risk reduction in people who are receiving ART is unknown.

### ***Vaccination to Prevent Reactivation Disease (Herpes Zoster)***

Two Food and Drug Administration (FDA)-approved vaccines are currently available for the prevention of herpes zoster in immunocompetent adults. In 2017, a subunit vaccine containing recombinant VZV glycoprotein E (gE) and adjuvant AS01B (i.e., recombinant zoster vaccine [RZV] Shingrix) was FDA approved and recommended by the Advisory Committee on Immunization Practices (ACIP) to prevent herpes zoster in immunocompetent adults aged  $\geq 50$  years, given on a 2-dose schedule.<sup>39</sup> The approval and recommendation for the vaccine were based on pivotal Phase 3 randomized, placebo-controlled clinical trials involving >30,000 participants in which the vaccine efficacy against herpes zoster in vaccinated participants was 97.2% overall and 91.3% in those aged  $\geq 70$  years.<sup>40,41</sup> The most common solicited adverse reactions in vaccine recipients were pain (78% of recipients), myalgia (45%), and fatigue (45%), with Grade 3 injection site reactions (pain, redness, and swelling) reported in 9.4% of vaccine recipients and Grade 3 solicited systemic events (myalgia, fatigue, headache, fever, and gastrointestinal symptoms) reported by 10.8% of vaccine recipients.<sup>39,42</sup> Systemic Grade 3 reactions were reported more frequently after Dose 2 than after Dose 1.<sup>42</sup>

Data on use of RZV in people with HIV are limited, and to date ACIP has not recommended the use of RZV in people with HIV. A Phase 1/2 randomized, placebo-controlled study enrolled 94 adults with HIV receiving ART<sup>43</sup> with CD4 count  $\geq 200$  cells/mm<sup>3</sup>, 14 adults receiving ART with CD4 count <200 cells/mm<sup>3</sup>, and 15 ART-naïve adults with CD4 count  $\geq 500$  cells/mm<sup>3</sup>. The participants' median age was 46 years. Participants received the vaccine in three doses administered at 0, 2, and

6 months. The vaccine increased humoral and cell-mediated immunity to VZV gE after two doses, including among people with CD4 counts <200 cells/mm<sup>3</sup>. The most common side effects included pain at the injection sites (98.6% of participants, 16.4% Grade 3), fatigue (75.3%, 16.4% Grade 3), myalgia (74.0%, 13.7% Grade 3), and headache (64.4%, 8.2% Grade 3). No vaccine-related severe adverse events occurred during follow-up. Based on these very limited data in people with HIV, the vaccine appears safe and immunogenic. No efficacy data are available for the RZV among people with HIV.

Given that the risk of herpes zoster is high among people with HIV, and the vaccine appears safe, experts recommend administration of RZV to people with HIV aged ≥50 years, following the FDA-approved schedule for persons without HIV (intramuscular [IM] dose at 0 and 2 months) **(AIII)**.

No data identify the optimal timing of vaccination for persons who have a CD4 count <200 cells/mm<sup>3</sup> or who are not suppressed virologically on ART. Following initiation of ART, some experts would administer the RZV vaccination series after CD4 count recovery **(CIII)**, and others would administer the series after virologic suppression was achieved **(CIII)**. No efficacy data guide RZV vaccination in people with HIV aged <50 years given the following:

- Clinical trial experience demonstrating safety in immunocompetent persons <50 years is limited, *and*
- The duration of protection is not known.

Thus, at this time, RZV **is not recommended** for people with HIV aged <50 years. RZV is not a treatment for herpes zoster and should not be given during acute episodes **(AIII)**. It also should not be given to individuals with VZV-related inflammatory eye disease (keratitis or anterior uveitis) during episodes of active inflammation **(AIII)**.

A 1-dose attenuated live-zoster virus vaccine (i.e., zoster vaccine live [ZVL], Zostavax<sup>®</sup>) for prevention of herpes zoster is FDA approved for use in immunocompetent adults aged ≥50 years. However, as of November 18, 2020, it is no longer available for use in the United States, and recommendations for its use have been removed from these guidelines.

## Treating Disease

### *Varicella*

No controlled prospective studies of antiviral therapy for varicella in adults with HIV have been reported. For uncomplicated varicella, the preferred treatment options are valacyclovir (1 g PO three times daily), or famciclovir (500 mg PO three times daily), initiated as early as possible after lesion onset and continued for 5 to 7 days **(AII)**. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) is an alternative **(BII)**. Intravenous (IV) acyclovir 10 mg/kg every 8 hours for 7 to 10 days is the recommended initial treatment for people with HIV with severe or complicated varicella **(AIII)**.<sup>15,48,49</sup> If no evidence of visceral involvement with VZV is apparent, many experts recommend switching from IV to oral antiviral therapy after the patient has defervesced **(BIII)**.<sup>50</sup>

### *Herpes Zoster*

Antiviral therapy should be instituted as soon as possible for all people with HIV with herpes zoster diagnosed within 1 week of rash onset (or any time prior to full crusting of lesions). The

recommended treatment options for acute localized dermatomal herpes zoster in people with HIV 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>51</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**). Adjunctive corticosteroid therapy for herpes zoster in people with HIV **is not recommended** because no data support its benefit in this population (**AIII**).

In patients with HZO, both stromal keratitis and anterior uveitis require treatment with topical corticosteroids; in many cases, chronic, low-dose topical corticosteroid therapy is necessary to maintain suppression of inflammation. Recurrences or exacerbations of inflammation are common. A role for antiviral agents in the management of chronic keratitis and uveitis has not been established.

ARN should be treated promptly with antiviral therapy. One treatment recommended by some experts is high-dose IV acyclovir (10 mg/kg every 8 hours for 10 to 14 days), followed by prolonged high-dose oral valacyclovir (1 g three times daily) (**AIII**). High-dose oral antiviral treatment for at least 14 weeks has been shown to decrease the risk of second eye involvement among those who present with unilateral ARN syndrome;<sup>52,53</sup> (**AIII**) however, many ophthalmologists and infectious disease specialists will continue oral antiviral therapy for much longer. Many experts would also include an intravitreal injection of ganciclovir as part of the initial induction therapy. Additional intravitreal injections can be given if there is concern for lack of treatment response, but injections should not be more frequent than twice weekly (**BIII**). Use of oral valacyclovir instead of IV acyclovir for initial treatment has been reported. This approach should be used with caution because serum drug levels with oral treatment will not be as high as those achieved with IV administration (**CIII**). Involvement of an experienced ophthalmologist in the management of patients with VZV ocular disease is strongly recommended (**AIII**).

Optimal antiviral therapy for PORN remains undefined and should be managed in consultation with an experienced ophthalmologist (**AIII**).<sup>54-56</sup> Outcomes with IV acyclovir or ganciclovir monotherapy were poor. Better results were obtained with IV ganciclovir (or the combination of ganciclovir plus foscarnet), along with intravitreal antiviral drug injections.<sup>24,55,57</sup> Specific treatment should include systemic therapy with at least one IV drug (either acyclovir or ganciclovir) (**AIII**) coupled with injections of at least one intravitreal drug (ganciclovir or foscarnet) (**BIII**).<sup>57,58</sup> 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. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy.

### ***When to Start Antiretroviral Therapy***

All people with HIV should receive ART as soon as possible after diagnosis of HIV infection. The presence of disease caused by VZV is not an indication to defer or discontinue ART (**AIII**).

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

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

Initiation of ART appears to be associated with an increased frequency of VZV reactivation, peaking at about 3 months after ART initiation.<sup>7,13,14,59,60</sup> Observational studies have shown the risk of herpes zoster to increase twofold to fourfold between 4 and 16 weeks after initiating ART. The clinical presentation and natural history of herpes zoster in the setting of immune reconstitution is similar to that observed in other people with HIV, and episodes of herpes zoster in either setting should be managed in the same manner.

### ***Managing Treatment Failure***

Treatment failure caused by resistance of VZV to acyclovir and related drugs (e.g., famciclovir, ganciclovir) is rare, but should be suspected when clinical findings do not improve within 7 days of initiation of therapy or when 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 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>61</sup> IV cidofovir is a potential alternative (**CIII**). Both foscarnet and cidofovir are nephrotoxic agents and should be given in consultation with an expert in infectious diseases.

### **Special Considerations During Pregnancy**

Pregnant women with HIV 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>36</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**).

For pregnant women without HIV with varicella, the risk of transmitting VZV to the infant resulting in congenital varicella syndrome is 0.4% when varicella infection occurs at or before 12 weeks' gestation, 2.2% with infection at 13 to 20 weeks, and negligible with infection after 20 weeks.<sup>62</sup> Women with varicella during the first half of pregnancy should be counseled about the risks to the fetus and offered detailed ultrasound surveillance for findings indicative of fetal congenital varicella syndrome.<sup>62</sup> Administration of VariZIG is recommended primarily to prevent complications in the mother; whether it has any benefit in prevention of congenital varicella syndrome is unknown. VariZIG should be administered to infants born to women who have varicella from 5 days before delivery to 2 days after delivery 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 pregnant women with HIV who have uncomplicated varicella during pregnancy (**BIII**). Pregnant women with HIV 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 herpes zoster in pregnant women with HIV is oral acyclovir or valacyclovir (**BIII**). Pregnant women should not receive the herpes zoster vaccine (**AIII**).

## Recommendations for Preventing and Treating Varicella-Zoster Virus Infections

### Pre-Exposure Prevention of VZV Primary Infection

#### Indications

- Adults and adolescents with HIV who have CD4 counts  $\geq 200$  cells/mm<sup>3</sup> and who do not have documentation of varicella vaccination, a history or diagnosis of varicella or herpes zoster confirmed by a health care provider, or laboratory confirmation of VZV disease; and anyone with HIV who is VZV seronegative should avoid exposure to persons with varicella or herpes zoster (**CIII**).

#### Vaccination

- Household contacts who are VZV-susceptible should be vaccinated to prevent potential transmission of VZV to at-risk people with HIV (**BIII**).
- In VZV-seronegative persons with CD4 counts  $\geq 200$  cells/mm<sup>3</sup>, administer primary varicella vaccination (Varivax™) in two doses (0.5 mL SQ) 3 months apart (**CIII**).
- If vaccination results in disease due to live-attenuated vaccine virus, treatment with acyclovir is recommended (**AIII**).
- If post-exposure VariZIG™ has been administered, wait  $\geq 5$  months before varicella vaccination (**CIII**).
- If post-exposure acyclovir has been administered, wait  $\geq 3$  days before varicella vaccination (**CIII**).
- Administration of varicella vaccine to severely immunocompromised people with HIV (CD4 counts  $< 200$  cells/mm<sup>3</sup>) is **contraindicated** (**AIII**).

### Post-Exposure Prophylaxis of VZV Primary Infection

#### Indications

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

#### Preferred Prophylaxis

- VariZIG 125 IU/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**)
- If post-exposure VariZIG has been administered, wait  $\geq 5$  months before varicella vaccination (**CIII**).

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

#### Alternative Prophylaxis (Begin 7 to 10 Days After Exposure)

- Acyclovir 800 mg PO 5 times daily for 5 to 7 days (**BIII**), or
- Valacyclovir 1 gm PO 3 times daily for 5 to 7 days (**BIII**)

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

### Preventing Herpes Zoster (Shingles)



## Recommendations for Preventing and Treating Varicella-Zoster Virus Infections

### *Vaccination*

Recombinant zoster vaccine (RZV, Shingrix) is the only available vaccine for prevention of shingles in the United States. As of November 18, 2020, attenuated zoster vaccine live (ZVL, Zostavax) is no longer available for use in the United States.

### *RZV*

Recommended in adults with HIV aged  $\geq 50$  years, regardless of CD4 count:

- RZV 0.5 mL IM injection—2-dose series at 0 and then at 2 to 6 months **(AIII)**.
- RZV should not be given during an acute episode of herpes zoster **(AIII)**.
- Following initiation of ART, some experts would delay RZV vaccination until patients are suppressed virologically on ART **(CIII)** or until CD4 count recovery **(CIII)** to maximize immunologic response to the vaccine.

## Treating Varicella Infections

### *Primary Varicella Infection (Chickenpox)*

#### Uncomplicated Cases

##### Preferred Therapy

- Valacyclovir 1 g PO 3 times a day **(AII)**, or
- Famciclovir 500 mg PO 3 times a day **(AII)**

##### Alternative Therapy

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

##### Duration

- 5 to 7 days

#### Severe or Complicated Cases

- Acyclovir 10 mg/kg IV every 8 hours for 7 to 10 days **(AIII)**
- May switch to oral famciclovir, valacyclovir, or acyclovir after defervescence if there is no evidence of visceral involvement **(BIII)**

### *Herpes Zoster (Shingles)*

#### Acute, Localized, Dermatomal

##### Preferred Therapy

- Valacyclovir 1,000 mg PO 3 times a day **(AII)**, or
- Famciclovir 500 mg PO 3 times a day **(AII)**

##### Alternative Therapy

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

##### Duration

## Recommendations for Preventing and Treating Varicella-Zoster Virus Infections

- 7 to 10 days; longer duration should be considered if lesions resolve slowly

### *Herpes Zoster Ophthalmitis (HZO)*

Late dendriform lesions of the corneal epithelium should be treated with systemic or topical anti-herpetic medications **(AIII)**.

### Extensive Cutaneous Lesion or Visceral Involvement

- Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident **(AII)**.
- Switch to oral therapy (valacyclovir 1 g 3 times a day, famciclovir 500 mg 3 times a day, or acyclovir 800 mg PO 5 times daily to complete a 10- to 14-day course) when formation of new lesions has ceased and signs and symptoms of visceral VZV infection are improving **(BIII)**.

### *Acute Retinal Necrosis (ARN)*

- Acyclovir 10mg/kg IV every 8 hours for 10 to 14 days, followed by valacyclovir 1 g PO 3 times a day for  $\geq 14$  weeks **(AIII)**. In addition, an intravitreal injection of ganciclovir (2 mg/0.05mL) can be given as a part of initial treatment, and injections can be repeated at a frequency of twice weekly until there is evidence of a treatment response **(BIII)**.<sup>1</sup> Involvement of an experienced ophthalmologist is recommended **(AIII)**.
- Use of oral valaciclovir instead of IV acyclovir for initial treatment has been reported, but this approach should be used with caution, because serum drug levels with oral treatment will not be as high as those achieved with IV administration **(CIII)**.

### *Progressive Outer Retinal Necrosis (PORN)*

- Involvement of an experienced ophthalmologist is strongly recommended **(AIII)**.
- Acyclovir 10 mg/kg IV every 8 hours or ganciclovir 5 mg/kg every 12 hours **plus** ganciclovir 2 mg/0.05 mL and/or foscarnet 1.2 mg/0.05 mL intravitreal twice weekly **(AIII)**.
- Optimize ARV regimen **(AIII)**.
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic responses in consultation with an ophthalmologist.

**Note:** Ganciclovir ocular implants are no longer commercially available.

**Key:** ARN = acute retinal necrosis; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte cell; HZO = herpes zoster ophthalmicus; IM = intramuscular; IU = international unit; IV = intravenous; IVIG = intravenous immunoglobulin; PO = orally; PORN = progressive outer retinal necrosis; RZV = recombinant zoster vaccine; SQ = subcutaneous; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus; ZVL = zoster vaccine live

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