Varicella-Zoster Virus Diseases

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Epidemiology

Most adults in the United States have immunity to varicella-zoster virus (VZV), either by natural immunity or, for most people born after 2005, as a result of vaccination against primary varicella-zoster infection (chickenpox).[1,2] Thus, primary varicella-zoster infection (chickenpox) is rare in adults, including those with HIV. Reactivation of latent VZV results in herpes zoster (shingles). In the general population, the incidence of herpes zoster is three to five cases per 1,000 person-years, with higher incidence seen in older adults and immunocompromised individuals. The incidence of herpes zoster was more than 15-fold higher in people with HIV in the era before antiretroviral therapy (ART), but was 3- to 4-fold higher in the era of effective ART.[3-6] The risk of herpes zoster is higher in those with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3 or with HIV viremia.[4,7-10] Several studies demonstrated that the risk of herpes zoster in adults with HIV is increased in the 6-month period after ART initiation, possibly via an immune reconstitution inflammatory syndrome (IRIS)–related mechanism.[4,11] The risk of developing herpes zoster is lower in individuals who have been vaccinated against reactivation (shingles).

Clinical Manifestations

The rash of primary varicella infection (chickenpox) 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 the 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.[12] The most common complication of varicella infection is secondary bacterial infection with *Staphylococcus* or *Streptococcus* spp.[13] Visceral dissemination, especially VZV pneumonitis, is well documented and is the most serious complication.[12] Varicella can rarely result in involvement of the central nervous system (CNS) or other viscera (e.g., meningitis, encephalitis, transverse myelitis, myocarditis, nephritis, hepatitis).

Herpes zoster (shingles) manifests as a painful cutaneous eruption in a dermatomal distribution, often preceded by prodromal pain, paresthesias, or pruritus. The most common sites for herpes zoster are the thoracic dermatomes (up to 50% of cases), followed by cranial nerve (10% to 20% of cases), cervical (10% to 20% of cases), lumbar (10% to 20% of cases), and sacral (2% to 8% of cases) dermatomes.[14] 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, though this timeline can be protracted in immunocompromised individuals. Crusts typically persist for 2 to 3 weeks. The syndrome of zoster sine herpete includes similar pain without a visible rash.

The probability of a recurrence of herpes zoster in immunocompetent people over age 50 years who are not vaccinated against shingles is roughly 1% per year in the first 10 years[15]; limited available

data in people with HIV shows a rate of 12% to 15% in the first year.[16] Herpes zoster typically does not recur in the same dermatome. When a patient presents with recurrent vesicular lesions in the same dermatome, alternative etiologies, particularly herpes simplex virus (HSV), should be considered and excluded. In the ART era, 6% to 12% of people with HIV report post-herpetic neuralgia as a complication following herpes zoster.[17-19]

Various VZV-related neurologic syndromes can occur, including CNS vasculitis or vasculopathy, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, and focal brain-stem lesions.[20]

Herpes zoster of the geniculate ganglion of the sensory branch of the facial nerve is called Ramsay Hunt syndrome, also known as herpes zoster oticus, and presents with painful rash in the external auditory canal, facial nerve palsy, and loss of taste on the anterior two-thirds of the tongue.

Herpes zoster involving the ophthalmic division of cranial nerve V1 (the first branch of the trigeminal nerve), known as herpes zoster ophthalmicus (HZO), can affect the eye. Vesicles on the tip of the nose (Hutchinson sign) are a clue to involvement of the nasociliary branch of V1, indicating potential ocular involvement. All patients with V1 herpes zoster should have an ophthalmologic exam. HZO can manifest in keratitis, anterior uveitis, or both. For keratitis, VZV initially infects the corneal epithelium and eventually progresses to the corneal stroma, which can result in scarring, neovascularization, or necrosis with loss of vision. Stromal keratitis can be chronic. VZV-associated anterior uveitis also tends to be chronic and can result in increased intraocular pressure or glaucoma, intraocular tissue scarring, and cataract development. Stromal keratitis and anterior uveitis may not develop immediately after the appearance of skin vesicles on the forehead and scalp; therefore, patients who had initial normal eye examinations should receive follow-up eye examinations, even after the skin lesions heal. Some patients with HZO may develop late, painful dendriform lesions of the corneal epithelium that contain virus, peaking at a median of 5 months after the onset of HZO, with the rate of further recurrences decreasing over time.[21,22]

CNS vasculopathy/vasculitis due to VZV infection of cerebral arteries can result in transient ischemic attack and ischemic or hemorrhage stroke, aneurysm, and dissection. Strokes often occur in atypical vascular distribution or in patients without classic risk factors for stroke. The risk of stroke is highest in the weeks to months following an episode of herpes zoster, and some studies have found that this increased risk persists beyond 1 year.[23-26] Risk is highest after cases of HZO and is somewhat ameliorated by use of antivirals for herpes zoster/HZO.[23,26] VZV vasculopathy/vasculitis has also been shown to occur in patients without a preceding herpes zoster rash.[27] Whether post–herpes zoster stroke rate or presentation is altered in people with HIV compared with the general population is not yet known.

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) are variants of necrotizing retinopathy caused by hematogenous VZV. Although ARN can occur in both immunocompetent and immunocompromised patients, PORN[28] occurs almost exclusively in patients with CD4 counts <100 cells/mm^3. 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.[29] PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.[30] Both ARN and PORN are associated with high rates of loss of vision.

People with HIV who have CD4 counts <200 cells/mm^3 or during early immune reconstitution are at highest risk of herpes zoster–related complications, including disseminated herpes zoster,[31] which has been defined as involving three or more dermatomes, having more than 20 vesicles outside the area of the primary and adjacent dermatomes, or manifesting in organ-invasive disease or CNS disease.[32,33] Rates of any ocular involvement, HZO, Ramsay Hunt syndrome, bacterial superinfection, disseminated zoster, and post-herpetic neuralgia are all increased in people with HIV.[34]

Diagnosis

The rashes of varicella (chickenpox) and herpes zoster (shingles) are typically distinctive in appearance and usually can be diagnosed clinically. In immunocompromised people, cutaneous varicella may be difficult to distinguish from cutaneous disseminated herpes zoster (as opposed to dermatomal herpes zoster). Herpes zoster in genito-sacral dermatomes can mimic genital ulcer diseases such as herpes simplex and mpox. In any case where diagnosis cannot easily be made based on clinical appearance of the rash, polymerase chain reaction (PCR) testing using swabs of deroofed vesicular lesion, vesicular fluid, biopsy, or even scabs should be completed for VZV and any competing diagnoses (sensitivity 95% to 100%).[35,36] If PCR is not available, direct fluorescent antibody (also known as DFA) or viral culture from these specimens can also be used, but they are limited by lower sensitivity.[35] If adequate clinical specimens cannot be obtained at the time of active infection, acute and convalescent titers for VZV could be helpful in retrospectively diagnosing infection.

Histopathology and PCR of blood or other fluids, such as cerebrospinal fluid (CSF) or vitreous humor, can aid with the diagnosis of VZV infections of visceral organs (e.g., meningitis, retinitis). In suspected CNS vasculitis/vasculopathy (e.g., in cryptogenic stroke with preceding herpes zoster), the presence of anti-VZV CSF antibodies is the most reliable diagnostic test; CSF PCR for VZV, CSF pleocytosis, magnetic resonance imaging showing ischemic lesions centered at gray-white matter junctions, and specialized vascular imaging showing segmental stenosis or occlusion of cerebral arteries are also supportive of the diagnosis.[27]

Preventing Exposure

Primary varicella is highly communicable via direct contact and aerosolization from vesicles and respiratory secretions, with an attack rate of 31% to 72% in unvaccinated children without prior infection, from an unvaccinated infected contact.[37] People with HIV who are nonimmune to VZV (i.e., people who have no history or diagnosis of chickenpox or shingles confirmed by a health care provider or laboratory, who are seronegative for VZV, and who have no documented history of vaccination against VZV) should avoid exposure to individuals with active varicella or herpes zoster **(BIII).**

Preventing Disease

Recommendations for Preventing Varicella-Zoster Virus Infections

Prevention of Varicella-Zoster Virus Primary Infection (Varicella)

Vaccination

- See the Varicella Vaccine section of the Immunization chapter.
- If varicella vaccination results in disease caused by vaccine virus (a rare event), therapy with valacyclovir (preferred), acyclovir, or famciclovir is recommended (AIII).

Post-exposure Prophylaxis

Indications (AII)

- Close contact with a person who has active varicella or herpes zoster, *and*
- Nonimmune to VZV (i.e., lack documentation of varicella vaccination, no history or diagnosis of varicella or herpes zoster confirmed by a health care provider or laboratory, or known to be VZV seronegative)

Preferred Prophylaxis

- VariZIG 125 IU/10 kg (maximum of 625 IU) IM administered as soon as possible (within 96 hrs) and within 10 days after exposure to a person with active varicella or herpes zoster (AIII). Some experts recommend administering a second dose to high-risk patients with additional exposure to varicella >3 weeks after initial administration.
- If post-exposure VariZIG has been administered, wait ≥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 7–10 Days After Exposure)

- Valacyclovir 1 g PO three times daily for 5 to 7 days (BIII), *or*
- Famciclovir 500 mg PO three times daily for 5 to 7 days (BIII), *or*
- Acyclovir 800 mg PO five times daily for 5 to 7 days (BIII)

Note: The efficacy of post-exposure varicella vaccination for people with HIV has not been studied and is not recommended (CIII). However, if varicella vaccine is given, it should not be administered within 24 hours after the last dose of valacyclovir, famciclovir, or acyclovir given for post-exposure prophylaxis (CIII).

Prevention of Herpes Zoster (Shingles)

Vaccination

- See the Herpes Zoster Vaccine section of the Immunization chapter.

Pregnancy Considerations

- Pregnant women with HIV who are susceptible to VZV or of unknown immune status and are in close contact with a person with active varicella or herpes zoster should receive VariZIG as soon as possible (preferably within 96 hours) and within 10 days after exposure to VZV (AIII).

- For infants born to women who have varicella, VariZIG should be administered 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). Consultation with a perinatal specialist is recommended with preterm birth or low birth weight infants.

Key: IM = intramuscular; IVIG = intravenous immunoglobulin; PO = orally; VariZIG = varicella-zoster immune globulin; VZV = varicella-zoster virus

Varicella

Varicella vaccination (two doses, administered 4 to 8 weeks apart) is recommended for VZV-susceptible people with HIV aged ≥18 years with CD4 counts ≥200 cells/mm^3 **(BIII).** For additional details on varicella vaccination to prevent primary infection, see the Varicella Vaccine section of the Immunization chapter.

If varicella vaccination results in disease caused by vaccine virus (a rare event), therapy with acyclovir, famciclovir, or valacyclovir is recommended **(AIII).** Valacyclovir is the prodrug of acyclovir and has improved oral bioavailability and allows for decreased dosing frequency compared to acyclovir, making it the preferred oral regimen.

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 nonimmune to VZV (i.e., lack documentation of varicella vaccination, no history or diagnosis of varicella or herpes zoster confirmed by a health care provider or laboratory, or known to be VZV seronegative), post-exposure prophylaxis with immunoglobulin or antivirals following known or suspected close contact VZV exposure is recommended **(AII).** Close contact is defined as residing in the same household or in a shared hospital room, face-to-face contact with an infectious individual with active varicella, or touching/hugging a person with disseminated zoster or exposed lesions.[38] Adolescents and adults with HIV who are susceptible to VZV (particularly those with CD4 counts <200 cells/mm^3) should receive VariZIG as soon as possible (preferably within 96 hours), but up to 10 days after exposure **(AIII).**[39] Some experts recommend administering a second dose to high-risk patients with additional exposure to varicella >3 weeks after initial administration. Given the cost of obtaining VariZIG, it is reasonable to confirm absence of VZV seroprotection (via immunoglobulin G) 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 from exposure to varicella than from localized herpes zoster. In the United States, VariZIG is commercially available from a broad network of specialty distributers. The duration of protection from VariZIG is at least 3 weeks. Patients receiving monthly infusions of high-dose intravenous immunoglobulin (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.[39]

A 5- to 7-day course of post-exposure acyclovir, famciclovir, or valacyclovir beginning 7 to 10 days after exposure (to align with peak viral replication) 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).**[40] Valacyclovir, the prodrug of acyclovir, has improved oral bioavailability and allows for decreased dosing frequency compared with acyclovir, making it the preferred oral regimen. Among VZV-susceptible immunocompetent children, post-exposure varicella vaccination has been shown to reduce the risk for varicella and is more effective than preemptive therapy with antiviral drugs; however, the efficacy of post-exposure varicella vaccination for people with HIV has not been studied and **is not recommended (CIII).**

If post-exposure varicella-zoster immune globulin (VariZIG) has been administered, an interval of at least 5 months is recommended before varicella vaccination **(CIII).**[39] If post-exposure acyclovir, famciclovir, or valacyclovir has been administered, an interval of at least 24 hours after the last dose is recommended before varicella vaccination **(CIII).**

Herpes Zoster

Administration of recombinant zoster vaccine (RZV) to people with HIV ≥18 years of age is recommended following the U.S. Food and Drug Association–approved schedule for people without HIV (intramuscular dose at 0 and 2–6 months) **(AIII).** For additional details on herpes zoster vaccination, see the Herpes Zoster Vaccine section of the Immunization chapter.

Pre-exposure Prophylaxis and Secondary Prophylaxis to Prevent Herpes Zoster (Shingles)

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 acyclovir 400 mg orally (PO) twice a day as secondary prophylaxis (or "suppressive therapy") administered to people with HIV/HSV-2 coinfection who were not taking ART, the relative risk of first episode of herpes zoster was reduced by 62%.[41] 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. Indefinite secondary prophylaxis can be considered for those with severe VZV disease but has not been studied **(CIII).**

Treating Disease

Recommendations for Treating Varicella-Zoster Virus Infections
Primary Varicella Infection (Chickenpox)
• Initiate treatment as early as possible after lesion onset. Uncomplicated Cases (Duration: 5–7 days) *Preferred Therapy* • Valacyclovir 1 g PO three times daily (AII), *or* • Famciclovir 500 mg PO three times daily (AII)

Alternative Therapy

- Acyclovir 800 mg PO five times daily (BII)

Severe or Complicated Cases (Duration: 7–10 days)

- Acyclovir 10 mg/kg IV every 8 hours (AIII)
- May switch to oral antiviral therapy (as above) after defervescence and clinical improvement if no evidence of visceral involvement exists (BIII)

Herpes Zoster (Shingles)

- Initiate therapy as soon as possible and within 1 week of rash onset, or any time prior to full crusting of lesions (AIII).

Acute, Localized, Dermatomal (Duration: 7–10 days)

Preferred Therapy

- Valacyclovir 1 g PO three times daily (AII), *or*
- Famciclovir 500 mg PO three times daily (AII)

Alternative Therapy

- Acyclovir 800 mg PO five times daily (BII)

Note: A longer duration should be considered if lesions resolve slowly (CIII).

Extensive Cutaneous Lesions or Visceral Involvement

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

Notes

- People with HIV with herpes zoster who did not previously receive RZV should be vaccinated after their episode resolves to provide protection from recurrent episodes (CIII). Vaccination is recommended any time between resolution of the primary episode and 1 year later if possible, but can be given at any point in the future, as well (CIII).
- All patients with V1 herpes zoster should have an ophthalmologic exam. Stromal keratitis and anterior uveitis might 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 (AIII).

Herpes Zoster Ophthalmicus

- Consultation with an ophthalmologist experienced in the management of patients with VZV ocular disease is strongly recommended (AIII).
- RZV should not be given to individuals with VZV-related inflammatory eye disease (i.e., keratitis or anterior uveitis) during episodes of active inflammation (AIII).
- Oral antiviral treatment as above for “Acute, Localized, Dermatomal” herpes zoster

Late Dendriform Lesions of the Corneal Epithelium

- If/when a patient is not receiving oral antivirals, topical antivirals should be administered until lesions are resolved (AIII).
  - *Trifluridine 1% eye drops:* 1 drop in affected eye every 2 hours while awake (maximum nine times per day) until complete re-epithelialization; then, 1 drop every 4 hours while awake (minimum five times per day) for an additional 7 days (BIII), *or*
  - *Ganciclovir 0.15% gel:* 1 drop to affected eye five times a day (every 3 hours while awake) until re-epithelialization has occurred; then, 1 drop three times a day for an additional 7 days (BIII)

Stromal Keratitis and Anterior Uveitis

- Alongside initial systemic antiviral treatment (as above for "Acute, Localized, Dermatomal"), topical corticosteroids should be administered (AII).
  - *Typical regimen using prednisolone acetate 1% drops:* 1 drop in affected eye every 2 hours while awake (maximum eight times daily) until clinical response; then, slow taper over many weeks if clinical improvement continues, eventually decreasing to 1–2 drops daily for at least 1 year (AII)

Suppressive Therapy

- Valacyclovir 1 g PO daily for 12 months to prevent development of new, or exacerbations of existing, keratitis lesions and uveitis (AII)

Acute Retinal Necrosis

- Consultation with an ophthalmologist experienced in the management of patients with VZV ocular disease is strongly recommended (AIII).

Initial Therapy

- Acyclovir 10 mg/kg IV every 8 hours for 10 to 14 days or until lesion is healing (AIII)
- Oral antiviral induction therapy is not recommended (CIII).
- A single adjunctive intravitreal injection of ganciclovir (2 mg/0.05 mL) can also be given as a part of induction treatment (BIII). Additional injections can be given if there is a concern about lack of treatment response, but injections should not be given more frequently than twice weekly (BIII).

Suppressive Therapy (Duration: ≥6 months)

Preferred Therapy

- Valacyclovir 1 g PO daily (AIII)

Alternative Therapy

- Acyclovir 800 mg PO twice daily (CIII)

Progressive Outer Retinal Necrosis

- Optimal antiviral therapy for PORN remains undefined and should be managed by an ophthalmologist experienced in the management of VZV ocular disease (AIII). Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic responses in consultation with an ophthalmologist.
- Acyclovir 10 mg/kg IV every 8 hours *or* ganciclovir 5 mg/kg IV every 12 hours (AIII), *plus*
- Intravitreal ganciclovir 2 mg/0.05 mL *or* intravitreal foscarnet 1.2 mg/0.05 mL weekly (BIII)

Note: Ganciclovir ocular implants are no longer commercially available.

Pregnancy Considerations
• For infants born to women who have varicella, VariZIG should be administered 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). • The time period for VariZIG administration may be extended for preterm infants born at <28 weeks gestation or who weigh <1,000 g at birth, because of concerns for more severe neonatal disease in preterm and low birth weight infants (BIII). Consultation with a perinatal specialist is recommended. • Oral acyclovir or valacyclovir are the preferred treatments for uncomplicated varicella during pregnancy (BIII). • Hospitalization and treatment with IV acyclovir (10 mg/kg every 8 hours) are appropriate in cases of severe varicella or exhibited signs or symptoms of VZV pneumonitis during pregnancy (AII).

Key: IV = intravenous; PO = orally; PORN = progressive outer retinal necrosis; RZV = recombinant zoster vaccine; VariZIG = varicella-zoster immune globulin; VZV = varicella-zoster virus

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 or famciclovir, initiated as early as possible after lesion onset and continued for 5 to 7 days **(AII).** Oral acyclovir is an alternative **(BII).** Intravenous (IV) acyclovir is the recommended initial treatment for people with HIV with severe or complicated varicella (e.g. pneumonitis, encephalitis) **(AIII).**[12,42,43] If no evidence of visceral involvement with VZV is apparent, and patient is clinically improving, many experts recommend switching from IV to oral antiviral therapy after the patient has defervesced **(BIII).**[44]

Herpes Zoster

Antiviral therapy should be instituted for all people with HIV with herpes zoster as soon as possible and within 1 week of rash onset, or any time prior to full crusting of lesions **(AIII).** 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 **(CIII).** Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. If cutaneous lesions are extensive or if visceral or CNS involvement is suspected, IV acyclovir should be initiated and continued until clinical improvement is evident **(AII).**[45] A switch from IV acyclovir to oral antiviral therapy (to complete a total 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).** All patients with V1 herpes zoster should have an ophthalmologic exam. 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 **(AIII).**

Involvement of an ophthalmologist experienced in the management of patients with VZV ocular disease is strongly recommended for all cases of ocular involvement **(AIII).** In cases of herpes zoster affecting the trigeminal nerve, antiviral treatment at the onset of cutaneous lesions reduces the incidence and severity of ophthalmic involvement. Initial antiviral treatment for HZO is the same as

for herpes zoster in other dermatomes. Topical antivirals are only indicated for late dendriform lesions of the corneal epithelium if/when the patient is not receiving oral antivirals and should be continued until resolution of lesions **(AIII).** Ophthalmic trifluridine drops **(BIII)** or ganciclovir gel **(BIII)** can be used, although limitations to each exist. While requiring treatment beyond 2 weeks is unlikely, using trifluridine beyond this time frame may result in toxicity to the corneal epithelium; ganciclovir can be cost prohibitive. Acyclovir ophthalmic ointment is also an appropriate option but is not currently available in the United States.

In patients with HZO, both stromal keratitis and anterior uveitis require treatment with topical corticosteroids alongside initial systemic antiviral treatment **(AII);** in many cases, chronic, low-dose topical corticosteroid therapy is necessary to maintain suppression of inflammation.[46] A typical regimen is prednisolone acetate 1% drops: 1 drop in the affected eye every 2 hours while awake (maximum eight times daily) until clinical response, followed by a slow taper over many weeks if clinical improvement continues, eventually decreasing to 1 to 2 drops daily for at least 1 year **(AII).** However, the dose and duration of drug therapy may change based on the stability of control and any corticosteroid-related local side effects, highlighting the need to involve an experienced ophthalmologist. Based on a clinical trial involving immunocompetent adults with histories of HZO, use of valacyclovir (1 g PO daily) for 1 year reduced the risk of new or worsening VZV-related corneal diseases (e.g., stromal keratitis, dendriform epithelial keratitis, endothelial keratitis) or anterior uveitis for as long as 18 months after the start of treatment (at 12 months hazard ratio [HR] 0.70; $P = 0.02$; at 18 months HR 0.72; $P = 0.02$). Treatment appeared to be more effective for those aged less than 60 years and those with more recent onset of HZO.[47] One year of valacyclovir (1 g PO daily) also reduced various measures of neuropathic pain associated with HZO through 18 months, especially among individuals aged less than 60 years.[47] These treatment effects are likely to be true in people with HIV as well; therefore, suppressive therapy with valacyclovir 1 g PO daily for 12 months is recommended to prevent the development of new, or exacerbations of existing, keratitis lesions and uveitis **(AII).**

ARN should be treated promptly with antiviral therapy. High-dose IV acyclovir (10 mg/kg every 8 hours) for 10 to 14 days or until evidence of lesion healing, followed by prolonged suppressive oral therapy with valacyclovir 1 g daily **(AIII)** for at least 6 months to decrease the risk of second eye involvement is recommended. Oral acyclovir 800 mg twice daily is an alternative suppressive therapy **(CIII).** An intravitreal injection of ganciclovir can be administered as part of induction therapy **(BIII).** Additional intravitreal injections can be given if there is a 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 but **is not recommended** because serum drug concentrations with oral treatment will not be as high as those achieved with IV administration **(CIII).**

Optimal antiviral therapy for PORN remains undefined and should be managed in consultation with an experienced ophthalmologist **(AIII).**[48-50] The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. Treatment should include urgent systemic therapy with one IV drug (acyclovir or ganciclovir) **(AIII)** coupled with injections of one intravitreal drug (ganciclovir or foscarnet) **(BIII).**[51,52] 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.

When to Start Antiretroviral Therapy

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

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 Disease, as well as Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections.

Initiation of ART is associated with an increased frequency of VZV reactivation during the first 6 months after ART initiation.[4,11] 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. ART should not be delayed or stopped due to risk of, or in the setting of, herpes zoster-immune reconstitution inflammatory syndrome **(AIII).**

Managing Treatment Failure

Although rare, treatment failure caused by resistance to acyclovir and related drugs (i.e., famciclovir, ganciclovir) 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 should be performed to establish antiviral drug susceptibility and to document the need for alternative therapy. Susceptibility testing for research purposes is available at The University of Alabama at Birmingham's Antiviral Screening Laboratory (sjames@uabmc.edu). For patients with suspected or proven acyclovir-resistant VZV infections, treatment with IV foscarnet is recommended **(AII).**[53] 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 or of unknown immune status and are in close contact with a person with active varicella or herpes zoster should receive VariZIG as soon as possible (preferably within 96 hours) and within 10 days[39] 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).** VAR is **contraindicated** during pregnancy **(AIII).** However, if found to be nonimmune during pregnancy and CD4 counts are ≥200 cells/mm^3, VAR should be administered immediately after delivery, with a subsequent dose administered at the 6-week postpartum visit **(AIII).**

For pregnant women without HIV with varicella, the risk of transmitting VZV to the infant, resulting in congenital varicella syndrome, is 0.84% when varicella infection occurs at or before 20 weeks gestation and 0.59% over the course of the entire pregnancy.[54] 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.[55] Administration of

VariZIG is recommended, primarily to prevent complications in the mother; whether it has any benefit in preventing congenital varicella syndrome is unknown. For infants born to women with varicella, VariZIG should be administered between 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).** The time period for VariZIG administration may be extended for preterm infants born at <28 weeks of gestation or who weigh <1,000 g at birth because of concerns for more severe neonatal disease in preterm and low birth weight infants **(BIII).** Consultation with a perinatal specialist is recommended.

Data on RZV vaccine (Shingrix) during pregnancy is insufficient. Consider administering after delivery **(BIII).** No controlled studies of antiviral therapy of herpes zoster during pregnancy have been reported. 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).**

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