



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

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

Epidemiology

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

The overall prevalence of KS was as high as 30% among patients with AIDS before the advent of effective antiretroviral therapy (ART).⁶ The incidence of KS, which increased nearly 10-fold in the United States between 1981 and 1987, began to gradually decline in 1987.⁷ Reasons for this reduction in KS incidence prior to the widespread availability of ART are likely to be multiple, including the deaths of patients with advanced AIDS who were most susceptible to KS, and the increasing use by HIV-infected individuals of antiviral drugs that may have activity against HHV-8 (zidovudine for the treatment of HIV; ganciclovir, foscarnet, and cidofovir use for treatment of CMV disease).⁸ Supporting the latter hypothesis, observational studies indicate that patients receiving ganciclovir or foscarnet (but not acyclovir) develop KS at a reduced rate.^{9–12} A more marked reduction in KS incidence occurred in 1996, shortly after the introduction of protease inhibitor-containing ART in the United States. Today the incidence of KS in the United States remains approximately 3-fold higher than before the HIV pandemic, and notably KS incidence has not declined in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.¹³ Primary effusion cell lymphoma and multicentric Castleman's disease remain rare.¹⁴

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

Clinical Manifestations

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

Diagnosis

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

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

Preventing Exposure

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

Preventing Disease

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

Treating Disease

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

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

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

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

Special Considerations When Starting ART

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

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

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

infected patients initiating ART.

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

Multicentric Castleman's disease: A small number of patients with HIV-associated multicentric Castleman's disease were also observed to have a clinical decompensation upon initiation of ART.^{33,34}

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

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

Preventing Recurrence

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

Special Considerations During Pregnancy

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

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

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

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

Mild-to-Moderate KS:

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

Advanced KS:

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

PEL:

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

MCD:

Preferred Therapy (in consultation with a specialist):

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

Alternative Therapy for MCD:

- Rituximab 375 mg/m² given weekly for 4–8 weeks, may be an alternative to, or used adjunctively with, antiviral therapy **(CII)**

Other Considerations:

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

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

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