Human Herpesvirus-8 Disease

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Epidemiology

The seroprevalence of human herpesvirus-8 (HHV-8)—also known as Kaposi sarcoma-associated herpesvirus (KSHV)—varies worldwide and is estimated to be 1% to 5% in the general U.S. population[1,2] compared with 10% to 20% in certain Mediterranean countries and 30% to 80% in parts of sub-Saharan Africa.[3] In the United States, men who have sex with men (MSM) and persons with HIV infection are at increased risk for HHV-8 infection. Among MSM without HIV infection, the seroprevalence ranges from 13% to 20% and HHV-8 seroprevalence increases to 30% to 35% among MSM with HIV infection.[4-6] Injection drug use may also be a risk factor for HHV-8 seropositivity,[7] although this association has not been consistently observed.[8]

HHV-8 is etiologically associated with all forms of Kaposi sarcoma (KS) including classic, endemic, transplant-related, and AIDS-related, as well as rare neoplastic disorders (primary effusion lymphoma [PEL] and solid organ variants) and the lymphoproliferative disorder known as multicentric Castleman's disease (MCD). Although the precise pathogenesis for these tumors remains unclear, infection with HHV-8 precedes their development.[9] Patients who are HHV-8 seropositive and exhibit HHV-8 viremia are at increased risk (approximately nine-fold) for developing KS relative to those without HHV-8 viremia.[10] HHV-8 viremia typically accompanies symptomatic episodes of multicentric Castleman's disease.[11]

The overall prevalence of KS in the U.S. was as high as 30% among patients with AIDS prior to the advent of effective antiretroviral therapy (ART).[12] The incidence of KS rose steeply in the United States between 1981 and 1987 and subsequently gradually declined.[13] Reasons for this reduction in KS incidence prior to the widespread availability of ART include the deaths of patients with advanced AIDS who were most susceptible to KS, and the increasing use by individuals with HIV individuals of antiviral drugs that may have had activity against HHV-8 (zidovudine for the treatment of HIV; ganciclovir, foscarnet, and cidofovir use for treatment of CMV disease).[14] Supporting the latter hypothesis, observational studies indicate that patients receiving ganciclovir or foscarnet (but not acyclovir) develop KS at a reduced rate.[15-18] A more marked reduction in KS incidence occurred beginning in 1996, shortly after the introduction of protease inhibitor-containing ART in the U.S. Despite these declines, KS is among the most common cancers among the AIDS population in the U.S.,[19] and HIV infection increases the risk of KS several thousand fold even in the ART era.[20] Notably, KS is a common cancer in many countries in sub-Saharan Africa,[21] fueled in part by the HIV pandemic, and incidence has not declined in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.[22,23] PEL and MCD remain rare relative to KS.[24,25]

KS and PEL are described most frequently among individuals with HIV exhibiting advanced immunosuppression (CD4 T lymphocyte [CD4] cell counts <200 cells/mm^3), although they may occur at any CD4 cell count. Recent reports of KS occurring at higher CD4 cell counts in the United States[26,27] 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. MCD may arise at any CD4 cell count.

Clinical Manifestations

Most individuals latently infected with HHV-8 are asymptomatic.[28] Immunocompetent children and organ transplant recipients infected with HHV-8 may develop a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS.[29,30] KS manifestations vary

widely, but most patients have nontender, hyperpigmented, macular or nodular skin lesions. Oral lesions occur in approximately one-third of patients[31] and are predictors of pulmonary involvement and less favorable treatment outcomes.[32-34] Lymphatic involvement is also common and may lead to debilitating lower extremity edema. Involvement of internal viscera occurs in up to 50% of cases and may be difficult to diagnose. Patients with visceral involvement may be asymptomatic, or manifest with shortness of breath, painless rectal bleeding or melena, and other non-specific pulmonary and gastrointestinal symptoms.[35-40]

PEL characteristically presents with effusions isolated within the pleural, pericardial, or abdominal cavities,[41] but mass lesions and "extracavitary" disease within skin, hematopoietic organs, and the gastrointestinal tract have been described.[42-44] MCD routinely manifests with systemic symptoms including fever and night sweats, and findings on examination including generalized adenopathy, fever and hepatosplenomegaly.[24,45] MCD may mimic other inflammatory conditions including sepsis, with hypotension, clinical evidence of a systemic inflammatory response, and progression to multi-organ failure.[24,46,47]

Another HHV-8- associated condition, the KSHV inflammatory cytokine syndrome (KICS), has been more recently described.[48-50] Patients with this syndrome display MCD-like inflammatory symptoms, but do not have pathological findings of MCD. Patients with KICS are frequently critically ill and demonstrate marked elevations in IL-6 and IL-10, as well as high plasma HHV-8 viral loads. KICS may contribute to the inflammatory symptoms seen in some patients with severe KS or PEL, and there may be significant clinical overlap between these conditions.

Diagnosis

The diagnoses of KS, MCD and PEL depend on cytologic and immunologic cell markers, as well as histology. Clinical diagnosis alone is not sufficient for KS, and tissue examination is needed to confirm the diagnosis.[51,52] Confirmation of these diagnoses is achieved through immunohistochemical staining of tumors with antibodies recognizing the HHV-8-encoded latency-associated nuclear antigen (LANA).[53,54] While not commercially available, diagnoses may also be confirmed utilizing polymerase chain reaction (PCR) to identify HHV-8 DNA within tumor tissue.[53,54] Use of serologic testing for HHV-8 antibodies is currently not indicated for either diagnostic testing or routine screening for HHV-8-related illnesses due to lack of standardization and poor sensitivity and specificity of these assays.[55] In addition, use of PCR to quantify HHV-8 in the peripheral blood has no established role in the diagnosis of KS, MCD, or PEL.[11]

HHV-8 Transmission/Preventing Exposure

The mode(s) of transmission of HHV-8 remains unclear, but epidemiologic and virologic data suggest that saliva is a source of infectious virus and may be an important route of transmission. Asymptomatic HHV-8 infection is often associated with HHV-8 shedding in the saliva and occasional shedding in genital secretions.[4,28,56] In a study of 50 HHV-8-infected MSM in the U.S., HHV-8 was detected by PCR in the saliva of 39% of participants and on more than 35% of days on which samples were obtained.[4] HHV-8 shedding is also common among persons in sub-Saharan Africa. Among HHV-8-infected adults without KS in Uganda, 22% had HHV-8 DNA detected in saliva and 3% in genital secretions; HHV-8 was also detected in saliva of 68% of commercial sex workers in Kenya.[57,58] Based on these observations, viral shedding may result in HHV-8 transmission to uninfected partners through behaviors associated with exposure to saliva or genital secretions. HHV-8 transmission through blood transfusion has been reported in Uganda, where HHV-8 is endemic;[59] however, studies from the U.S. and Western Europe have not found evidence to support HHV-8 transmission through blood transfusion.[60,61]

Recommendations to prevent exposure to HHV-8 do not yet exist; screening patients for HHV-8 serostatus or behavioral modifications to limit potential exposures have not been validated and are not currently recommended**.**

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 treatments outweighs the potential use for prophylaxis **(AIII).** Because strong risk factors for the development of KS in HIV-positive individuals include both low CD4-positive T cell count[62] and uncontrolled viremia,[63] early initiation of ART is likely to be the most effective measure for the prevention of KS **(AII)**. Although epidemiologic data are somewhat conflicting, there are no antiretroviral agents which have proven clearly superior for the prevention of KS.[60-65] Therefore, specific classes of ART for prevention of KS or other HHV-8-associated illnesses are not recommended **(AII)**.

Treating Disease

KS: Chemotherapy, in combination with ART, should be administered to patients with visceral involvement **(AI)** and is likely to be a useful adjunctive therapy in individuals with disseminated cutaneous KS **(BIII)**.[64-67] Liposomal doxorubicin and paclitaxel exhibit comparable response rates and progression-free survival, although liposomal doxorubicin exhibits less high-grade toxicity relative to paclitaxel and is, therefore, generally preferred as first-line therapy **(AI).**[64] Paclitaxel has proven effective with relapse following treatment failure with liposomal doxorubicin.[67] Importantly, concurrent use of corticosteroids in patients with KS should be either avoided or used with caution and under close observation, given the potential for exacerbation of life-threatening disease, as well as an association between the use of corticosteroids and development of KS **(AIII)**.[68-70] KS arising in the setting of organ transplantation is related to the use of corticosteroids and other non-targeted immunosuppressives, especially in geographic areas of high HHV-8 seroprevalence.[71] Transplant-associated KS may be effectively treated or avoided with use of immunosuppressive regimens which include drugs that inhibit the mammalian target of rapamycin (mTOR) such as rapamycin and sirolimus.[71-73]

The antiviral agents ganciclovir, foscarnet, and cidofovir exhibit *in vitro* activity against HHV-8.[74,75] Available data indicate that antivirals have limited efficacy for the treatment of KS (ganciclovir and cidofovir)[76,77] and HHV-8-associated hemophagocytosis (foscarnet).[78,79] Therefore, antiviral agents with activity against HHV-8 are not recommended for KS treatment **(AII)**.

PEL: Chemotherapy, in combination with ART, should be administered to patients with PEL (**AIII**), although, given its rarity, there are limited data available from longitudinal observational series or prospective randomized clinical trials. The combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in combination with ART has demonstrated some benefit, albeit still limited, for PEL, and the combination of infusional etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) demonstrated superior survival relative to CHOP in one pooled analysis **(BII)**.[80,81] Rituximab may be considered for rare CD20-positive cases of PEL **(CIII)**, and dose-adjusted EPOCH (DA-EPOCH) may be beneficial for some patients **(CIII)**.[82,83] Antiviral agents, including valganciclovir or zidovudine, may also be used as adjunctive therapies, but available data are limited for this approach and additive toxicities may limit their utility **(CIII)**.[84-86]

MCD: There are no standardized treatments for MCD, but several treatment regimens have been utilized. The use of either IV ganciclovir or oral valganciclovir are options for treatment of MCD **(CII).** A 3-week course of twice-daily IV ganciclovir or oral valganciclovir was associated with remissions in MCD in one report,[87] and a combination of valganciclovir and high-dose zidovudine has led to durable clinical remissions **(CII)**.[88]

Rituximab has also emerged as an important adjunctive treatment for MCD **(CII)**,[89,90] although up to one-third of patients receiving rituximab may have subsequent exacerbations or emergence of KS.[91,92] For patients with concurrent diagnoses of KS and MCD, use of both rituximab and liposomal doxorubicin is recommended **(BII)**.[45] Therapeutic monoclonal antibodies targeting either interleukin-6 (IL-6) or the IL-6 receptor have also proven effective for some patients with MCD and may be utilized in some situations **(BII)**.[93-95] At this time, there is insufficient evidence to recommend monitoring IL-6 levels for diagnostic or prognostic purposes. Although corticosteroids are potentially effective as an adjunctive therapy for MCD, they should be used with caution or avoided, especially in patients with concurrent KS, given potential for exacerbation of life-threatening KS **(AIII)**.[68-70]

Detailed recommendations for the 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 with appropriate guidance from both oncology and infectious disease specialists **(AIII).** Preferred ART to be given concurrently with chemotherapy for HHV-8 malignancies should be chosen to minimize drug-drug interactions and additive toxicities.

Special Considerations When Starting Antiretroviral Therapy

Early initiation of ART may prevent incident KS and PEL.[74,96] ART that suppresses HIV replication should be administered to all patients with HIV and KS **(AII)**, PEL **(AIII)**, or MCD **(AIII)**, 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) may occur among HHV-8-infected patients initiating ART.

KS: KS-IRIS is characterized by either first presentation of KS ("unmasking"), or paradoxical worsening of pre-existing KS following ART initiation, and can be associated with significant morbidity and mortality.[97] Studies in the U.S. and Europe reveal that KS is the most commonly reported form of IRIS, occurring in 6% to 34% of KS patients with HIV who are initiating ART.[98,99] In sub-Saharan Africa, exacerbations of KS compatible with KS-IRIS have been reported in 18% to 61% of adults initiating ART treatment.[100-102] Risk factors for developing KS-IRIS include advanced KS tumor stage (T1), pre-treatment HIV viral load >5 $\log_{10}$ copies/mL, detectable pre-treatment plasma HHV-8, and initiation of ART alone without concurrent chemotherapy.[97] Treatment of KS-IRIS includes systemic chemotherapy and supportive measures. Steroids are strongly discouraged for management of KS-IRIS, as corticosteroid therapy has been associated with exacerbation of pre-existing KS in persons with HIV **(AIII)**.[70,103]

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

MCD: A small number of patients with HIV-associated MCD have experienced clinical decompensation upon initiation of ART.[104,105]

Although neither the incidence nor predictors of HHV-8-associated IRIS are well-described, 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 patients with HIV and KS may prevent KS progression or occurrence of new lesions. Because KS is an AIDS-defining cancer, ART is indicated for all patients with active KS **(AII).** Suppression of HIV replication to prevent recurrence is also recommended for patients with MCD **(AIII)** as well as those with malignant lymphoproliferative disorders **(AIII).**

Special Considerations During Pregnancy

The seroprevalence of HHV-8 infection among pregnant women with HIV 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.[106] Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels,[107] although levels of HHV-8 DNA in the peripheral blood may increase late in pregnancy.[108] HHV-8 seropositivity does not appear to influence pregnancy outcome. Routine screening for HHV-8 by PCR or serology is not indicated for pregnant women with HIV **(AIII).** Antiviral therapy for HHV-8 infection in pregnancy is not recommended **(AIII).** Given the rarity of KS, PEL, and MCD in pregnancy and the potential toxicity of the drugs used for treatment, when these conditions occur in pregnancy, they should be managed with consultations between the obstetrician, infectious disease specialist, and oncologist. With limited disease, treatment may be deferred until after delivery.[109]

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.[110-113] 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,[114,115] higher risk for transmission with higher maternal antibody titer (and, by inference, higher maternal levels of HHV-8),[116] and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants.[117] Data indicate increased mortality through age 24 months among infants with HIV born to HHV-8-seropositive mothers compared with HHV-8-seronegative mothers,[114-116,118-123] but these studies could not completely account for other confounding factors affecting infants with HIV. 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.[118-123]

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

Preventing development of KS:

- Since low CD4 cell count and uncontrolled HIV viremia are strong risk factors of KS, early initiation of ART is likely to be the most effective measure for the prevention of KS **(AII)**

Mild-to-Moderate KS (localized involvement of skin and/or lymph nodes)[1]:

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

Advanced KS (visceral and/or disseminated cutaneous disease)[1]:

- Chemotherapy (*in consultation with specialist*) + ART [visceral KS **(AI)** or widely-disseminated cutaneous KS **(BIII)**].
- Liposomal doxorubicin is preferred first-line chemotherapy (**A1**)
- Avoid use of corticosteroids in patients with KS, including those with KS-IRIS, given the potential for exacerbation of life-threatening disease (**AIII**)
- Antiviral agents with activity against HHV-8 are not recommended for KS treatment (**AIII**).

PEL:

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

MCD:

All patients with MCD should receive ART **(AIII)** in conjunction with one of the therapies listed below.

Therapy Options (in consultation with a specialist, and depending on HIV/HHV-8 status, presence of organ failure, and refractory nature of disease):

- IV ganciclovir (or oral valganciclovir) +/- high dose zidovudine (**CII)**
- Rituximab +/- prednisone **(CII)**
- For patients with concurrent KS and MCD – rituximab + liposomal doxorubicin **(BII)**
- Monoclonal antibody targeting IL-6 or IL-6 receptor **(BII)**
- Corticosteroids are potentially effective as adjunctive therapy, but should be used with caution or avoided, especially in patients with concurrent KS. **(AIII)**

Other Considerations:

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

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intraveneously; KS = Kaposi sarcoma; MCD = multicentric Castleman's disease; PEL = primary effusion lymphoma; PO = orally; q(n)h = every "n" hours

[1] The commonly used AIDS Clinical Trials Group (ACTG) KS Staging Classification uses T(Tumor), Immune(I), and Systemic illness (S) criteria to classify patients into "Good Risk" and "Poor Risk" categories (ref Krown, JCO, 1989). "Good Risk" tumor stage criteria are used by some specialists to correspond with mild-to-moderate KS.

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