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 3% to 7% in the general U.S. population[1-4] compared with 16% in China,[5] 10% to 20% in several Mediterranean countries, and 30% to more than 90% in parts of sub-Saharan Africa.[6-10] In the United States, men who have sex with men (MSM) and people with HIV are at increased risk for HHV-8 infection.[11,12] Among MSM without HIV, the HHV-8 seroprevalence ranges from 13% to 20%, and it increases to 30% to 68% among MSM with HIV, with particularly high rates among MSM in the southern United States.[13,14] Injection drug and methamphetamine use may also be a risk factor for HHV-8 seropositivity,[15] although this association has not been observed consistently.[11-13,16]

HHV-8 is etiologically associated with all forms of Kaposi sarcoma (KS), including classic, endemic, transplant-associated, and HIV-associated (also known as "epidemic" KS). HHV-8 causes a plasmablastic form of multicentric Castleman's disease (MCD), which is a lymphoproliferative disorder. HHV-8 is also associated with primary effusion lymphoma (PEL), both its effusion-based and extra cavitary forms. Approximately 80% of PEL cases are also coinfected with Epstein-Barr virus.[17] Another type of HHV-8-associated lymphoma is known as HHV-8 positive diffuse large B-cell lymphoma (HHV-8 DLBCL), not otherwise specified.[18] Although the precise pathogenesis for these tumors remains unclear, infection with HHV-8 precedes their development.[19] HHV-8 is also related to an inflammatory syndrome known as KSHV-associated inflammatory cytokine syndrome (KICS), which is a diagnosis of exclusion.[20]

The overall prevalence of KS in the United States was as high as 30% among patients with AIDS prior to the advent of effective antiretroviral therapy (ART).[21] The incidence of KS rose steeply in the United States between 1981 and 1987 and then gradually declined, even prior to the widespread availability of highly effective combination ART.[22] Considerable geographic disparity of KS exists within the United States and worldwide. Higher rates of KS occur in the southern United States,[23] where higher mortality has been reported among Black men than in other populations.[14,24] KS is a common cancer in sub-Saharan Africa,[25] where it presents as epidemic and endemic KS. Importantly, KS incidence has declined only modestly in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.[26-28] PEL and MCD remain rare relative to KS[29,30]; however, the rarity of these conditions may be related to underdiagnosis.

Clinical Manifestations

Most individuals latently infected with HHV-8 are asymptomatic.[31] Immunocompetent children and organ transplant recipients newly infected with HHV-8 may develop a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS.[32,33]

KS: KS manifestations vary widely, but most patients have nontender, hyperpigmented, macular or nodular skin lesions. Oral lesions occur at initial presentation in approximately one-quarter of

people[34,35] and are predictors of pulmonary involvement and less favorable treatment outcomes.[36-39] Lymphatic involvement is also common and may lead to debilitating lower extremity edema, even after successful treatment with chemotherapy. Persistent lymphedema, particularly of the legs, may be complicated by reduced mobility, contractures, diffuse serous drainage, skin ulceration, and recurrent cellulitis.[40,41] Involvement of internal viscera occurs in up to 50% of cases and may be difficult to diagnose. Patients with visceral involvement may either be asymptomatic or manifest with shortness of breath, painless rectal bleeding or melena, or other nonspecific pulmonary and gastrointestinal symptoms.[42-47] Involvement of organs, including the brain and heart, and extensive lytic bone lesions can also occur.[48,49] Of note, KS lesions can occur on the eyelid skin or conjunctiva. In one study conducted prior to the introduction of potent ART, 20 of 100 individuals with AIDS and KS had ophthalmic lesions.[50] In some individuals, eyelid or conjunctival lesions will be the first and initially the only clinically apparent site of KS.

MCD: MCD routinely manifests with systemic symptoms, including fever and night sweats, and findings upon examination, including generalized adenopathy, fever, and hepatosplenomegaly.[29,51] MCD may mimic nonspecific inflammatory conditions, including sepsis with hypotension and laboratory abnormalities associated with a systemic inflammatory response such as cytopenia (thrombocytopenia, anemia) and low albumin, and progress to multi-organ failure if untreated.[29,52,53] The clinical manifestations of MCD can be relapsing and remitting in nature. HHV8-associated MCD occurs in people with HIV with concurrent KS (cutaneous and/or visceral) in up to 50% of cases and can occur at high CD4 T lymphocyte (CD4) cell counts.[54]

PEL: PEL characteristically presents with effusions isolated within the pleural, pericardial, or abdominal cavities,[55] but mass lesions and "extra cavitary" disease within skin, hematopoietic organs, and the gastrointestinal tract have been described.[56-58] Patients with PEL may also present with concurrent KS (either cutaneous and/or visceral KS) and/or MCD, which may complicate diagnosis and treatment.

HHV-8 DLBCL: This type of lymphoma typically involves lymph nodes but can disseminate to extranodal sites.[59-61] Patients present with fevers and night sweats, with evidence of systemic inflammation. Patients may have massive splenomegaly as HHV-8 DLBCL may arise concurrently with MCD.[62]

KICS: KICS has been described primarily in patients with concurrent KS.[20,63,64] In the initial report of this syndrome, patients had specific signs and symptoms associated with inflammation and displayed MCD-like inflammatory symptoms but did not have pathological findings of MCD. Patients with KICS frequently are critically ill and demonstrate marked elevations in interleukin-6 (IL-6) and interleukin-10, as well as high plasma HHV-8 viral loads. It is important to note that patients with PEL meet criteria for KICS, but as a distinct pathologic process with unique oncologic management, it is essential to appropriately work up and exclude PEL among individuals who meet KICS criteria.[65] Therefore, KICS is a diagnosis of exclusion, and it is essential to rule out other HHV-8 conditions, including both MCD and PEL, which have different treatment paradigms.[66]

Overlapping HHV-8 Disorders: KS can present concurrently with MCD, PEL, or KICS. Individuals with MCD may have a concurrent lymphoma or KS at presentation or experience the emergence of KS following MCD treatment.[67] Consequently, a thorough diagnostic workup (including imaging and histologic evaluation) must be undertaken to appropriately diagnose any other concurrent HHV8-associated disorders, as treatment may vary depending on the diagnosis.

Diagnosis

Kaposi Sarcoma

Clinical diagnosis alone generally is not sufficient for KS, and tissue examination is needed to confirm diagnosis.[68,69] Diagnosis of KS requires histologic confirmation of suspected KS lesions. KS diagnosis is confirmed by immunohistochemical (IHC) staining of tumors with antibodies recognizing the HHV-8-encoded latency-associated nuclear antigen (LANA). Polymerase chain reaction (PCR) to identify HHV-8 DNA within tumor tissue may augment IHC, but the role of PCR in KS diagnosis remains under evaluation.[70,71] In settings where biopsy is not available, referral to a center where a biopsy can be safely obtained is important.

Bronchoscopy for visualization of endobronchial KS lesions and CT of the chest should be performed if there is concern for pulmonary KS (respiratory symptoms or abnormal chest X-ray); however, transbronchial biopsies or biopsies of endobronchial lesions are not recommended because of the vascular nature of these tumors and risk of bleeding. CT abdomen and upper endoscopy and colonoscopy should be performed if there is suspicion for gastrointestinal (GI) KS (GI symptoms, iron deficiency anemia, or positive fecal occult blood). GI biopsy of KS lesions is feasible and important for establishing the diagnosis of KS or other opportunistic infections, such as cytomegalovirus, which may impact management. Conjunctival KS remains a clinical diagnosis due to potential complications of obtaining conjunctival biopsies.

Kaposi Sarcoma Staging

The AIDS Clinical Trials Group (ACTG) criteria is the most widely used KS staging system and is based on tumor extent (T), immunologic status as measured by CD4 count (I), and the presence of systemic illness (S). “Good risk” tumor stage (T0) is defined as KS confined to the skin and/or lymph nodes and/or minimal oral disease. “Poor risk” tumor stage (T1) is defined as KS with tumor-associated edema and/or ulceration, extensive oral disease, or visceral KS.[72,73]

Multicentric Castleman’s Disease

The diagnosis of MCD requires a lymph node biopsy. Histology demonstrates monotypic, lambda restricted plasmablasts that are HHV-8-infected (LANA positive) and are primarily located in the mantle cell zones and/or abutting the germinal centers.[59] Lymph node biopsies may also demonstrate concurrent KS. Research studies examining flow cytometry studies of peripheral blood and effusions from patients with MCD during episodes of flare have shown HHV-8 positive lambda restricted plasmablasts or viroblasts that may be indicative of this diagnosis.[74,75] Histologic biopsy of lymph nodes remains the standard for MCD diagnosis.

Primary Effusion Lymphoma

PEL diagnosis requires measurement of cytologic and immunologic cell markers by flow cytometry analyses, as well as histology confirmation for cases of suspected extracavitary PEL.

HHV-8 Diffuse Large B-Cell Lymphoma

HHV-8 DLCBL requires pathologic confirmation of involved nodal or extranodal sites.

KSHV-Associated Inflammatory Cytokine Syndrome

KICS may occur concurrently in patients with KS. Criteria for KICS include:

1. Clinical manifestations
    a. Symptoms (e.g., fever, fatigue, respiratory and/or gastrointestinal symptoms)
    b. Laboratory abnormalities (e.g., pancytopenia, low albumin)
    c. Radiographic abnormalities (e.g., organomegaly, body cavity effusions, lymphadenopathy)
2. Evidence of systemic inflammation (elevated C-reactive protein)
3. Elevated HHV-8 DNA levels in the plasma or peripheral blood mononuclear cells (PBMCs)
4. Absence of a pathologic diagnosis of MCD or PEL, which would require lymph node assessment or sampling of body cavity effusions

The working KICS criteria requires the presence of at least two clinical manifestations drawn from at least two different categories (1a, b, and c) and meeting criteria 2 through 4.[20,76]

Other Diagnostic Considerations for HHV-8-Related Disease

Serologic testing for HHV-8 antibodies is not used for either diagnostic testing or routine screening for HHV-8-related illnesses. The lack of a standardized role for HHV-8 serology is in part due to the poor sensitivity and specificity of the current assays.[77]

Measurement of plasma HHV-8 is useful for diagnosis and monitoring of some HHV-8-related diseases. In one study from South Africa, patients with KS with elevated HHV-8 viral levels in the blood were often associated with S1 stage, or the presence of systemic illness, and indicative of a concurrent HHV-8 inflammatory syndrome.[78] A prospective study in Uganda also found that a higher HHV-8 copy number in plasma at KS diagnosis was associated with worse survival outcomes in epidemic and endemic KS.[79] For patients with KICS, detection of HHV-8 in blood is part of the diagnostic criteria.[80] HHV-8 DNA levels in the PBMCs are elevated in patients with active MCD and PEL,[17,80,81] and an undetectable plasma HHV-8 DNA may exclude a diagnosis of MCD.[80] Among patients with MCD, PBMC HHV-8 DNA levels decrease following a flare.[67] A retrospective study demonstrated that whole blood HHV-8 DNA levels appeared to be higher in patients with MCD than in patients with KS.[82]

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.[31,83,84] In a study of 50 MSM with HHV-8 infection in the United States, HHV-8 was detected by PCR in the saliva of 39% of participants on more than 35% of days on which samples were obtained.[83] HHV-8 shedding is also common among persons in sub-Saharan Africa. Among adults with HHV-8 without KS in Uganda, 22% had HHV-8 DNA detected in saliva and 3% in genital secretions; HHV-8 also was detected in saliva of 68% of commercial sex

workers in Kenya.[85,86] 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.[13] HHV-8 transmission through blood transfusion has been reported in Uganda, where HHV-8 is endemic[87]; however, studies from the United States and Western Europe have not found evidence to support HHV-8 transmission through blood transfusion.[88,89] Perinatal transmission from the placenta or during delivery or peripartum also occurs.

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

Recommendation for Preventing Development of Kaposi Sarcoma
• Administer ART to all people with HIV to reduce the likelihood that KS will develop (AI).

Key: ART = antiretroviral therapy; KS = Kaposi sarcoma

Because strong risk factors for the development of KS in people with HIV include both low CD4 count[90] and uncontrolled viremia,[91] the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) recommends early initiation of ART to reduce the risk of KS **(AI).**[92,93] Although epidemiologic data are somewhat conflicting, no antiretroviral agents have proven clearly superior to others for the prevention of KS.[88-91,94,95]

Although ganciclovir inhibits HHV-8 replication, insufficient evidence exists to support the use of ganciclovir for prophylaxis of HHV-8 disease.[96] Therefore, the Panel recommends against the use of ganciclovir or valganciclovir in preventing HHV-8 disease **(AIII).**

Treating Disease

Recommendations for Treating HHV-8-Associated Diseases—Kaposi Sarcoma, Primary Effusion Lymphoma, Multicentric Castleman's Disease
General Treatment Considerations
• Treatment for HHV-8-associated diseases should be undertaken in consultation with guidance from both oncology and infectious disease specialists, with additional input from centers specifically caring for people with HIV and cancer (AIII).
• Among people with HIV, all HHV-8-specific treatments should be given with ART, which is an essential component of managing these diseases (AI).
• ART given concurrently with chemotherapy for HHV-8 malignancies should be chosen to minimize drug–drug interactions and additive toxicities (AIII).
Kaposi Sarcoma
ACTG StageT0 (localized involvement of skin and/or lymph nodes and/or minimal oral disease only):
• ART (AII) alone, *or*
• ART plus liposomal doxorubicin (AIII), if disease does not respond to ART alone; *or*

ACTG stage T1 [extensive and/or symptomatic KS skin lesions, extensive oral disease, tumor-associated edema, and/or ulceration or any visceral involvement]:

- Preferred Therapy
  - ART plus liposomal doxorubicin (AI)
- Alternative Therapy
  - ART plus paclitaxel, if liposomal doxorubicin is not available (AI), or to treat recurrence after treatment with liposomal doxorubicin (AII), *or*
  - ART with oral pomalidomide plus thromboprophylaxis (e.g., low-dose aspirin 81 mg daily) (BII)

Note: Concurrent use of systemic corticosteroids or other immunosuppressants in patients with KS should either be avoided or used under close observation, given the potential for exacerbation of KS (AIII).

Multicentric Castleman's Disease

Preferred Therapy

- MCD without KS: ART plus rituximab (BII)
- MCD with KS: ART plus rituximab with liposomal doxorubicin (AII)

Alternative Therapy

- ART plus IV ganciclovir (or oral valganciclovir) with or without high-dose zidovudine—not for use in cases of multi-organ failure, such as renal and/or hepatic failure (CII)

Primary Effusion Lymphoma or HHV-8 Diffuse Large B-Cell Lymphoma (with or without KS)

Preferred Therapy

- PEL or HHV-8-associated DLBCL: ART plus combination chemotherapy, such as EPOCH (AIII)
- PEL or HHV-8-associated DLBCL with MCD: ART plus dose-adjusted EPOCH and rituximab (CII)

KSHV-Associated Inflammatory Cytokine Syndrome

- After excluding MCD and PEL, ART plus rituximab with combination chemotherapy for concurrent KS (CII)

Key: ACTG = AIDS Clinical Trials Group; ART = antiretroviral therapy; DLBCL = diffuse large B-cell lymphoma; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin combination therapy; HHV-8 = human herpesvirus 8; IV = intravenous; KS = Kaposi sarcoma; KSHV = Kaposi sarcoma–associated herpesvirus; MCD = multicentric Castleman's disease; PEL = primary effusion lymphoma; T1 = "Poor risk" tumor stage

General Treatment Considerations for All Patients With HHV-8-Associated Disorders

Treatment for HHV-8-associated diseases should be undertaken in consultation with an experienced specialist with appropriate guidance from both oncology and infectious disease specialists with additional input from centers specifically caring for people with HIV and cancer **(AIII).** Among people with HIV, all HHV-8-specific treatments should be given with ART, which is an essential component of managing these disorders **(AI).** ART given concurrently with chemotherapy for HHV-8 malignancies should be chosen to minimize drug–drug interactions and additive toxicities **(AIII).** Consider referral for clinical trials for all HHV-8-associated disorders, including patients with persistent or recurrent KS.

Kaposi Sarcoma

Initiating ART alone, without chemotherapy, can effectively treat KS in people with HIV with ACTG T0 tumor stage (limited cutaneous KS and no visceral disease) and is therefore recommended as initial therapy **(AII).**[97] Of note, a multicenter trial in sub-Saharan Africa and South America found that initiating ART in combination with chemotherapy (oral etoposide) reduced the risk of suspected KS-immune reconstitution inflammatory syndrome (IRIS) and/or early KS progression compared with ART alone, but it did not provide durable clinical benefit as measured by death, KS progression, or initiation of chemotherapy, other than etoposide.[98,99] Liposomal doxorubicin, along with ART, can be administered in consultation with a specialist in cases where T0 tumor stage disease does not resolve with ART alone **(AIII).**

Chemotherapy, in combination with ART in people with HIV, should be administered in patients with ACTG T1 tumor stage, defined as extensive and/or symptomatic KS skin lesions, extensive oral disease, tumor-associated edema and/or ulceration, or any visceral involvement of KS **(AI).**[79,94,95,98,100,101]

Although liposomal doxorubicin and paclitaxel exhibit comparable response rates and progression-free survival, liposomal doxorubicin exhibits less high-grade toxicity relative to paclitaxel.[94] In limited resource settings, where liposomal doxorubicin is not available, data have demonstrated benefits in using paclitaxel over other available regimens, such as bleomycin and vincristine or etoposide.[102] Therefore, liposomal doxorubicin is recommended as first-line therapy **(AI);** when liposomal doxorubicin is unavailable, paclitaxel is a recommended alternative **(AI).** Paclitaxel is also recommended to treat recurrent KS following treatment with liposomal doxorubicin **(AII).**[100]

Pomalidomide, an oral immunomodulatory drug, has been investigated in patients with KS with and without HIV. Among people with HIV, pomalidomide was approved for use by the U.S. Food and Drug Administration if KS is not responsive to ART alone **(BII).** Pomalidomide was administered with ART and aspirin 81 mg (for thromboprophylaxis) with response rates of 67% among people with HIV in a Phase 1/2 study.[103] In this study, 83% of participants had received prior chemotherapy at baseline. Adherence to oral therapy and thromboprophylaxis is important while using pomalidomide.

KS may be recurrent despite ART adherence and re-treatment with the same systemic KS treatment options may be feasible. However, for patients with persistent or worsening KS despite chemotherapy, other concurrent HHV-8 diseases, specifically PEL or MCD, should be considered **(BIII).**

Local Therapy

For individuals with large, bulky eyelid or conjunctival lesions, local treatment may be necessary to improve eyelid function, relieve associated pain, and prevent complications from ocular surface exposure. In cases of stage T0 disease, local treatments of eyelid or conjunctival lesions reported to be effective include surgical excision, cryotherapy alone, low-dose radiation, and topical or intralesional injections of interferon-alfa-2a or -2b **(CIII).**[50,104-106] Each approach has been reported to cause complete lesion regression, with minimal side effects, but no comparative studies have been reported that identify the most effective local treatment. Similarly, for stage T0 skin disease, local therapies have been used.[107,108] However, these studies were done prior to the introduction use of

effective ART. Overall, as KS may recur despite local therapies, options for systemic therapy should be sought, especially in cases with T1 disease **(AI).**

Other Agents

Concurrent use of systemic corticosteroids or other immunosuppressants in patients with KS should either be avoided or used under close observation, given the potential for exacerbation of KS **(AIII).**[109-111]

The antiviral agents ganciclovir, foscarnet, and cidofovir exhibit *in vitro* activity against HHV-8.[112,113] Available data indicate that these antiviral drugs have limited efficacy for the treatment of KS[114,115] and HHV-8-associated hemophagocytosis.[116,117] Therefore, antiviral agents with activity against HHV-8 are not recommended for KS treatment **(AII).**

Multicentric Castleman's Disease

Rituximab is recommended as first-line treatment for MCD **(BII),**[118,119] although up to one-third of patients receiving rituximab may have subsequent exacerbations or emergence of KS.[120,121]

For patients with concurrent diagnoses of KS and MCD, use of both rituximab and liposomal doxorubicin is recommended **(AII).**[51,67]

Other Agents

Monoclonal antibodies targeting either IL-6 or the IL-6 receptor are approved for patients with idiopathic MCD, but this is not applicable in patients with HHV8-associated MCD.[122-124] Use of tocilizumab in HHV-8-associated MCD resulted in five of eight participants having a response in MCD; however, duration of the response was only 3.2 months, and seven of the study participants received rituximab for subsequent MCD flares.[125] Currently, insufficient evidence exists to recommend monitoring IL-6 levels for diagnostic or prognostic purposes.

A 3-week course of twice-daily intravenous (IV) ganciclovir or oral valganciclovir was associated with remissions in MCD in one report,[126] and a combination of valganciclovir and high-dose zidovudine (ZDV) has led to durable clinical remissions[127]; therefore, IV ganciclovir or oral valganciclovir may be considered when treating MCD without multi-organ dysfunction, either with or without high-dose ZDV **(CII).** Additionally, studies have explored the role of maintenance oral valganciclovir with tocilizumab or ZDV with valganciclovir and rituximab-based therapies. Among those treated with rituximab with liposomal doxorubicin and maintenance ZDV/valganciclovir, the 5-year progression-free survival was 89%.[67] The role of maintenance therapies in MCD is unclear given the relapsing and remitting nature of this disease, and they are therefore not recommended.

Although corticosteroids appear to be 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).**[109-111] In patients with MCD who have emergence of KS or worsening KS, KS-directed therapy should be continued beyond MCD management **(BII).**[128]

Primary Effusion Cell Lymphoma and HHV-8 Diffuse Large B-cell Lymphoma

Combination chemotherapy regimens used for other B-cell lymphomas, in combination with ART, should be administered to patients with PEL with curative intent **(AIII).** Due to the rarity of this

disease, limited data are available from 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. The combination of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) demonstrated superior survival relative to CHOP in one pooled analysis [129,130] Therefore, ART with EPOCH should be given as first-line treatment for PEL or HHV-8 DLBCL with or without concurrent KS **(AIII).**

Rituximab and dose-adjusted EPOCH **(CII)** should be considered in patients with PEL or HHV8-DLBCL and concurrent diagnosis of MCD with or without concurrent KS [131,132] One retrospective observational study of 20 patients (19 treated with EPOCH regimen with or without rituximab, bevacizumab, and/or high-dose methotrexate as combinations) has shown a 3-year cancer-specific survival of 47%.[17]

KSHV-Associated Inflammatory Cytokine Syndrome

Because of the overlapping clinical and laboratory features between KICS and MCD, rituximab in combination with chemotherapy has been evaluated as a therapeutic option for KICS, which is commonly observed with concurrent KS. This has led to improvement in clinical symptoms in case reports and case series.[76,133] In a larger prospective evaluation of patients with KICS, in 18 patients administered rituximab in combination with chemotherapy for concurrent KS, 55% of patients had a response per the clinical benefit response criteria, which includes laboratory findings and symptoms associated with KICS.[66] Therefore, rituximab with combination chemotherapy to treat KS is recommended for patients with KICS **(CII).** As rituximab is associated with the onset or deterioration of KS, careful management of concurrent KS is imperative.

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

When initiating ART, IRIS may occur among patients with HHV-8-related KS, PEL, or MCD.

KS: KS-IRIS is characterized by either first presentation of KS ("unmasking") or paradoxical worsening of pre-existing KS and can be associated with significant morbidity and mortality.[134] Studies in the United States and Europe reveal that KS is the most commonly reported form of IRIS, occurring in 6% to 29% of patients with KS and HIV who are initiating ART.[135,136] In sub-Saharan Africa, exacerbations of KS compatible with KS-IRIS have been reported in 18% to 31% of adults initiating ART.[137-139]

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.[134,135] Therefore, an accurate staging of KS prior to starting ART without chemotherapy is necessary.

Treatment of KS-IRIS includes systemic chemotherapy and supportive measures. Steroids are strongly discouraged for managing KS-IRIS because corticosteroid therapy has been associated with exacerbation of pre-existing KS in people with HIV **(AIII).**[111,140]

KS may present concurrently with other HHV-8 diseases, such as PEL, MCD, or KICS, which may mimic features of KS-IRIS.

MCD and PEL: Little information exists about the frequency of IRIS in terms of unmasking or paradoxical worsening of MCD or PEL.[136,141]

Preventing Recurrence

ART should be continued lifelong as with all people with HIV. Suppression of HIV replication may prevent recurrence and is recommended for patients with KS and MCD **(AIII),** as well as those with HHV-8-associated 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 2.4% to 6.0% among pregnant women from four other U.S. cities.[142,143] One study from Brazil of 131 pregnant women with HIV found HHV-8 antibodies in 0.8% and no HHV-8 DNA was detected.[144] However, given the much higher HHV-8 prevalence and occurrence of KS among African populations[3], including among pregnant women,[145] clinicians should have a lower threshold for consideration of HHV-8-related diagnoses with consistent clinical presentations among pregnant African immigrants with HIV. Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels,[146] although levels of HHV-8 DNA in the peripheral blood may increase late in pregnancy.[147] HHV-8 seropositivity does not appear to influence pregnancy outcome.

Routine screening for HHV-8 by PCR or serology is not recommended during pregnancy **(AIII).**

Antiviral therapy with cidofovir, ganciclovir, or foscarnet or other antivirals targeting 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 among the obstetrician, infectious disease specialist, and oncologist. With limited disease, treatment may be deferred until after delivery.[148]

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.[149-152] Perinatal transmission of HHV-8 occurs infrequently. Evidence supporting perinatal transmission during pregnancy or the intrapartum period includes cases of KS occurring in the infant shortly after birth,[153,154] higher risk for transmission with higher maternal antibody titer (and, by inference, higher maternal levels of HHV-8),[155] and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants.[156] Maternal HIV infection was associated with decreased transplacental transfer of antibodies to HHV-8 and lower cord blood levels of HHV-8 antigens, as compared to mothers without HIV; however, there was no effect on age of infection in the child.[157] Data indicate increased mortality through age 24 months among infants with HIV born to HHV-8-seropositive mothers compared with HHV-8-seronegative mothers,[153-155,158-163] 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 women compared with HHV-8 antibody-negative women.[158-163]

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