Kaposi sarcoma (KS) is a multifocal angioproliferative disorder of vascular endothelium, primarily affecting mucocutaneous tissues with the potential to involve viscera. Four clinical variants of classic, endemic, iatrogenic, and epidemic KS are described for the disease, each with its own natural history, site of predilection, and prognosis. In the absence of therapy, the clinical course of KS varies from innocuous lesions seen in the classic variant to rapidly progressive and fatal lesions of epidemic KS.

Classic KS is a rare and mild form of the disease first described by the Hungarian dermatologist Moritz Kaposi in the 19th century as a vascular tumor affecting the lower extremities of elderly men from the Mediterranean region. Although primarily detected in the Eastern European and Mediterranean basin, pockets of this variant in other geographic regions have also been reported. The male-to-female ratio for classic KS is 17:1, and lesions primarily present as multiple purplish-red pigmented plaques on the skin of arms, legs, and trunk of men older than 50 years in the endemic areas. Lesions tend to start on the extremities, progressively enlarge, and spread to more proximal sites. Classic KS has an indolent course, often spares viscera, and does not require aggressive therapy. There is evidence that some patients with classic KS may be at a greater risk for development of solid or hematopoietic neoplasms.

Iatrogenic KS refers to the form associated with the use of steroids, immunosuppressive agents, and drugs with antitumor necrosis factor (TNF) activity in patients with autoimmune disorders, inflammatory conditions, or solid organ transplantation. Interestingly, the incidence of KS following bone marrow (BM) or peripheral blood stem cell (PBSC) transplantation is low with only a few cases reported in the literature. Iatrogenic KS has a 3:1 male predilection, may involve mucocutaneous tissues, lymph nodes, or viscera; and tends to affect liver transplant patients more often than recipients of kidney or heart allografts. Although no clear association between dose or duration of immunosuppressive therapy and development of iatrogenic KS has been reported, discontinuation of therapy appears to improve iatrogenic KS.

African or endemic KS is a variant of disease affecting human immunodeficiency virus (HIV)-seronegative children and young adults in sub-Saharan Africa. Following the HIV epidemic, the incidence of this variant has increased significantly, particularly in the pediatric population, in the African subcontinent. The clinical course of endemic KS is variable and includes indolent skin disease, locally infiltrative lesions of extremities, and aggressive visceral involvement with potentially fatal sequelae. Generalized lymphadenopathy is a common feature of endemic KS, and oral mucosa is infrequently affected.

Epidemic or acquired immunodeficiency syndrome (AIDS)-associated KS (AIDS-KS) is the most common variant and a more aggressive form of this disorder. It is also the second-most frequent tumor affecting HIV patients worldwide, known to have an unfavorable prognosis in the absence of therapy. The incidence of epidemic KS is correlated with the mode of HIV acquisition and in the western hemisphere, HIV-seropositive male ho-
mosexuals are 5 to 10 times more at risk for KS compared with other groups with high-risk behaviors.\(^34\) This is in stark contrast with Africa, where AIDS-KS affects younger age groups and both genders, albeit unequally.\(^39\)

Although epidemic KS may develop throughout the entire spectrum of HIV disease, it is more likely to occur in the context of advanced immunosuppression,\(^6\) and could represent the first manifestation of HIV infection in some patients.\(^15\) Lesions of AIDS-KS tend to enlarge, multiply in number, become more nodular, or coalesce in association with immune deterioration and drop in CD4 count.\(^40\) Epidemic KS often affects mucocutaneous tissues as multifocal plaques, patches, and nodules with a predilection for the face and lower extremities (Figs. 1 and 2).\(^1,6,41,42\)

More than half of patients with AIDS-KS may have visceral involvement.\(^34\) Manifestation of AIDS-KS in the gastrointestinal tract may occur independent of skin disease and lead to abdominal pain, diarrhea, weight loss, bleeding, and vomiting when symptomatic.\(^1,34\) Pulmonary KS, the second-most common site of extracutaneous KS, is a late and potentially fatal complication presenting with cough, dyspnea, and hemoptysis in symptomatic patients.\(^1,43,44\) Asymptomatic pulmonary KS may manifest with abnormal radiographic findings on chest x-ray, which could be differentiated from opportunistic infections by gallium and thallium scans.\(^34,45\) Lymphedema, a complication resulting from obstruction of lymphatics, frequently affects the lower extremities and periorbital region of HIV patients.\(^15,41\) It may develop before or concurrent with diagnosis or progression of KS\(^36\) and, in the context of AIDS-KS, indicates advanced disease and poor prognosis.\(^6,32,46,47\)

**MANIFESTATION OF KS IN THE ORAL CAVITY**

All forms of KS may present in the oral cavity; however, oral lesions are more likely to occur with the epidemic variant of the disease.\(^5,9,11,36,48,49\) The oral cavity is the first clinical site of disease in 22% of patients with KS,\(^5,36,50-52\) and up to 71% of HIV patients may develop oral KS concurrent with cutaneous and visceral involvement.\(^5,36\) Oral KS may also be the initial indication of undiagnosed HIV infection.\(^9,15,36\) The most frequently affected oral sites include hard palate, gingival, and dorsal tongue (Figs. 3 and 4).\(^7,15,36\) Oral KS may present as solitary, multifocal, or multicentric macules, plaques, or nodules of different sizes, varying in color from deep red to bluish-purple. Multifocal lesions may gradually coalesce into confluent, exophytic masses affecting oral mucosa.\(^36,53\) Resorption of alveolar bone underlying KS and tooth mobility,\(^54,55\) primary intraosseous KS of the jaw bones,\(^52\) and involvement of major salivary glands have also been documented.\(^34,56\) Oral KS may cause local tissue destruction, pain, bleeding, difficulty with mastication, or interference with wearing of oral prosthesis.\(^5,7\) Development of KS in the oral cavity also has prognostic implications for untreated HIV patients,\(^15,57\) who are found to have higher death rates than patients affected only by cutaneous disease.\(^37,58\)

**ROLE OF KSHV IN KS PATHOGENESIS**

The pathogenesis of KS involves infection with human herpes virus type 8 (HHV-8), also known as Kaposi sarcoma–associated herpes virus (KSHV).\(^31\) KSHV is a DNA virus first isolated by Chang et al.\(^59\) from the KS lesion of an AIDS patient in 1994. It is believed to be the infectious agent necessary for development of all clinical subtypes of KS irrespective of
differences in presentation, natural history, or prognosis. The finding that KSHV induces angiogenic and inflammatory cytokines, as well as gene products implicated in angiogenesis, may suggest a direct role for this virus in KS pathogenesis. Also, viral load of KSHV in lesions positively correlates with clinical progression of KS from patch/plaque to the nodular stage. The etiologic role for KSHV is further supported by higher risk of KS development in KSHV-infected solid organ transplant recipients and HIV-seropositive patients. Regression of iatrogenic KS with the cessation of immunosuppressive therapy also indicates KSHV may be an essential but insufficient cofactor in KS pathogenesis.

In HIV-seropositive patients, detection of KSHV DNA in peripheral blood and in mononuclear cells of peripheral blood is shown to predict onset of KS. In men coinfected with both HIV and KSHV, the KS hazards appear to increase by 60% for each year of infection with HIV and KS pathogenesis probably involves a synergistic action between these viruses. It is postulated that HIV-mediated immune suppression/dysregulation promotes T-helper type-1 cytokines, such as TNF-alpha, interleukin-1b (IL-1b), and IL-6. Production and release of HIV-Tat protein from HIV-infected cells further contribute to release of proinflammatory cytokines, vascular endothelial growth factors (VEGFs), and matrix metalloproteinases (MMPs), facilitating proliferation of endothelial cells and development of KS. HIV-Tat protein and chronic state of inflammation also mediate reactivation and replication of latent KSHV, promoting expression of viral gene products implicated in angiogenesis. In this postulate, coinfection with HIV and KSHV in the presence of a chronic inflammatory state is conducive to initiation and progression of KS. This model is, however, incomplete, as KS also develops in HIV-seronegative patients, indicating that contribution of HIV gene products is not critical in all variants of KS.

KSHV SEROPREVALENCE AND MODE OF TRANSMISSION

Seroprevalence of KSHV among the general population varies geographically and its precise mode of transmission is not clearly understood. KSHV has been detected in a variety of body fluids and potential routes of transmission include vertical, horizontal through sex or oral shedding, blood transfusion, and injection drug use, as well as solid organ or BM transplantation. The pathogenesis of iatrogenic
KS may involve transmission of KSHV from the infected graft or reactivation of KSHV in seropositive recipients in the context of immunosuppression.49,72

In regions where KSHV infection is endemic, infection is probably acquired in childhood from seropositive family members and seroprevalence rates increase with age reaching as high as 80%.71,75-77

The drop in the mean age of onset and loss of male predilection for AIDS-KS in the African subcontinent have been attributed to high KSHV seroprevalence among HIV-seronegative residents of sub-Saharan Africa and superimposition of AIDS-KS on the preexisting risk of endemic KS in these regions.13,34,38,77,78 In view of both spread of the HIV epidemic in Africa and poor access to highly active antiretroviral therapy (HAART), infected patients often develop rapidly progressive KS with life expectancy of fewer than 6 months.34,79

Several studies suggest mode of transmission may affect risk of KSHV infection.80,81 In a cohort of HIV-seronegative males from Brazil, KSHV seroprevalence was higher among men who have sex with men (MSM) compared with males with an intravenous drug use habit, suggesting a sexual route for KSHV transmission.82 Smith and coworkers81 identified homosexual/bisexual but not heterosexual behavior as the independent risk factor for KSHV seropositivity among 2718 patients attending a sexually transmitted diseases clinic. Distribution pattern of KSHV seropositivity also mirrors that of sexually transmitted pathogens and HIV-infected homosexuals have higher prevalence of KSHV antibodies compared with HIV-seronegative MSM.88,82,83

Despite the evidence in support of a sexual route of transmission for HHV-8,80,81 a number of studies support a role for saliva and saliva-contaminated objects for transmission of KSHV between immunocompetent MSM.84,85 For instance, KSHV has been detected more frequently and at a higher viral load in saliva compared with genital and anal specimens collected from a group of homosexual males.84 Also, higher copy numbers of KSHV in saliva compared with semen have been found in patients with and without KS and independent of HIV status.86 Moreover, saliva samples from HIV-infected Kenyan women more often tested positive for KSHV DNA than plasma or vaginal swabs.87 It is possible that oropharyngeal epithelial cells harbor KSHV and facilitate its replication and shedding into saliva, contributing to viral transmission.84,88,89

**KS HISTOLOGY AND DIAGNOSIS**

KS lesions clinically resemble vascular entities and vary in color from pink to reddish-purple.32 Although mucocutaneous discoloration is a classic feature of KS, isolated nonpigmented oral lesions have been documented.90,91 Differential diagnosis of clinical mucocutaneous lesions includes nevi, pyogenic granuloma, bacillary angiomatosis, hemangioma, angiosarcoma, and, when affecting bone-bearing oral tissues, also melanoma, leukemia, and lymphoma, as well as inflammatory or fibrotic gingival enlargements,5,7,92-95 necessitating histopathological tissue evaluation for definitive diagnosis.5,5

Microscopic features of KS are diagnostic and shared by all variants of the disease (Fig. 5).96 They include an abundance of proliferating mononuclear inflammatory and spindle cells, ill-defined vascular channels, hemorrhage, and edema.9,60 Hemorrhage may result from the absence of smooth muscle cells known as pericytes in the newly formed blood vessels, causing leakage and erythrocyte extravasation.90 Histopathological features of KS become more prominent with clinical progression from the early patch to plaque and more advanced nodular form of the disease.7,33 Microscopically, this is manifested as a transition from focally proliferative miniature vessels to tumorlike fascicles mainly composed of spindle cells and vascular network, as well as atypical and extravasated erythrocytes.94,92

In early lesions, the spindle cell component may be sparse, leading to misdiagnosis of KS as a benign vascular lesion.5 In addition, bacillary angiomatosis (BA) caused by Bartonella henselae, shares similar clinical and microscopic features with early KS.1,4 Demonstration of the etiologic agent by Warthin-Starry silver stain or a positive therapeutic response to doxycline, however, help exclude this infectious entity.1,97 Identification of KSHV DNA by polymerase
chain reaction (PCR) or immunohistochemistry and detection of KSHV latency-associated nuclear antigen (LANA) have been proposed for differentiation of KS from clinically similar lesions.6,7,9,8 Diagnosis of KS in a patient with unknown HIV status mandates evaluation for the presence of coexisting HIV infection.9,11 HIV-seropositive patients with lesions suggestive of KS should receive a diagnostic biopsy for confirmation.6 Initial workup for staging AIDS-KS involves a complete physical examination that includes evaluation of skin, oral cavity, and rectum, as well as a chest x-ray.6 When pulmonary or gastrointestinal disease is suspected, lesions may be visualized by bronchoscopy or endoscopy, respectively.6 Presence of additional symptoms or physical and laboratory findings may necessitate other diagnostic workup.6 Clinical features of lesions, such as color, surface features, and, in particular, presence of nodularity and KS-associated edema should also be documented at each visit.6

**PATHOGENESIS OF KS**

Lesions of KS are composed of a heterogeneous population of cells expressing a variety of antigenic profiles.7,24,26,31,99 For example, the endothelial cells of KS express both lymphatic and vascular immunophenotypes.7 KS lesions test positive for CD-34, a glycoprotein expressed on blood vascular endothelium,100 and C-kit, expressed on both vascular and lymphatic endothelium.101 The evidence for lymphatic expression of endothelial cells includes positivity for D2-40,102-104 a highly sensitive and specific marker of podoplanin glycoprotein that is not expressed on vascular endothelium.105 The current opinion suggests that infection of endothelial cell precursors by KSHV may lead to a cascade of intracellular events conducive to a hyperinflammatory state, angiogenesis, and lymphatic differentiation.35,102 The pathogenesis of lymphedema in AIDS-KS may involve cytokine-driven local inflammation, KSHV-induced proliferation of lymphatic endothelial cells, obstruction of lymphatic channels, and enlargement of affected lymph nodes.106

There is no consensus on whether KS represents a true malignant neoplasm derived from monoclonal expansion of a single neoplastic progenitor cell; a multicentric, reactive, polyclonal, angioproliferative disorder; or both.10,33,107 Although the monoclonal nature of advanced nodular lesions arising in different body parts has been demonstrated by several investigators,108,109 a number of questions remain unresolved. These include variable course of KS lesions, the absence of classic features of malignancy,7 rarity of metastasis or anaplastic transformation, absence of cytogenetic abnormalities even with established monoclonality,10,111 and the potential for spontaneous regression,15,32 particularly with the start of HAART,112-114 all of which point to a reactive virus-induced angioproliferative pathogenesis.115

Proponents of this concept argue that disseminated KS probably results from multicentric proliferation of KSHV-infected endothelial cells at different sites rather than true metastatic spread as expected from a malignant process.15,108 Although early lesions may result from reactive polyclonal hyperplasia driven by inflammatory mediators,31,46,60,63 persistent cellular proliferation also increases the risk of mutations leading to dysregulated growth.69 Clinically aggressive KS could potentially represent malignant transformation of a subset of monoclonal cells within advanced lesions.6,31,46,109 Future studies will help clarify whether KS represents a malignant neoplasia or an inflammatory hyperplasia.99

**MANAGEMENT STRATEGIES**

Selection of therapeutic interventions for KS depends on the location and variant of KS; the rate of progression and distribution of lesions; the presence, absence, or severity of symptoms; the efficacy and potential side effects of therapy; the presence or absence of HIV infection and comorbidities; the degree of host immune competence; and the prognosis and preference of the patient.3,4,6,34,116 Therapy for KS aims to palliate symptoms, reduce tumor-associated edema, and improve esthetics and function.32,36,41,42,106 Therapeutic approaches for classic KS range from no treatment to surgical excision, local interventions, and radiotherapy.11,33 Management of iatrogenic KS often involves reduction or elimination of immunosuppressive therapy with or without local measures,3,4,32,117 whereas epidemic KS is frequently responsive to systemic chemotherapy.3,32 Management of epidemic KS, in contrast, is not aimed at a cure but palliation and control of KS progression with HAART is considered an essential component of this process.6,34,106,116

**AIDS-KS AND HAART**

There is evidence that epidemic KS often regresses with HAART112-114,118 and that HIV patients undergoing antiretroviral therapy have a less severe form of the disease compared with those naive to HAART at the time of KS diagnosis.57,58,119 Potent antiretroviral medications have, in fact, led to a dramatic decline in the incidence of KS among patients infected with HIV.6,120 The criteria for staging epidemic KS, with the advent of HAART, have also been modified.1 The current prognostic indicators for staging of AIDS-KS, proposed by Nasti et al.,121
include tumor extension (T) and HIV-related systemic illness (S) resulting in good and poor survival risk categories depending on the combination of prognostic markers (Table I). In this modified classification, severity of immunosuppression reflected in CD4 count is not an independent prognostic indicator for staging AIDS-KS as initially put forth by the AIDS Clinical Trials Group (ACTG) Oncology Committee.\textsuperscript{1,121,122} In the post-HAART study by Nasti et al.,\textsuperscript{121} treated HIV-positive patients with the combination of poor tumor stage (e.g., tumor-associated edema) and constitutional symptoms (T\textsubscript{1}S\textsubscript{1}) were found to have an unfavorable prognosis with a 3-year survival rate of 53%. In contrast, HIV patients on HAART with none or only 1 prognostic criteria (T\textsubscript{0}S\textsubscript{0}, T\textsubscript{0}S\textsubscript{1}, T\textsubscript{1}S\textsubscript{0}) were found to have a good prognosis with 3-year survival rates of 88%, 80%, and 81%, respectively.\textsuperscript{121} In addition, within the T\textsubscript{1} risk category, pulmonary involvement was predictive of poorest survival.\textsuperscript{121}

Suppression of viral replication and restoration of immunity by HAART has proven efficacious in control of disease in most patients considered to have good prognosis (T\textsubscript{0}S\textsubscript{0}, T\textsubscript{0}S\textsubscript{1}, T\textsubscript{1}S\textsubscript{0}).\textsuperscript{1,34,124} Based on review of 9 prospective studies, Krown\textsuperscript{124} found that institution of antiretroviral therapy alone led to resolution of early lesions of epidemic KS in 80% of patients. Initiation of HAART in newly diagnosed patients or intensification of medical therapy in those resistant to or compliant with antiretroviral therapy is, therefore, indispensable to treatment of HIV-KS.\textsuperscript{6,34,106} Nevertheless, some clinicians advocate watchful waiting or consideration of CD4 cell count, viral load, and active opportunistic infections prior to HAART initiation for asymptomatic KS (T\textsubscript{0}S\textsubscript{0}, T\textsubscript{1}S\textsubscript{0}).\textsuperscript{1,124,125} Despite these observations, HAART alone is not sufficient for advanced epidemic KS with poor prognostic index (T\textsubscript{1}S\textsubscript{1}), which requires additional interventions.\textsuperscript{1,34,124,126-128} When tolerable, AIDS-KS with unfavorable prognosis (e.g., pulmonary involvement or rapidly progressive disease) is best managed with a combination of HAART and systemic chemotherapy.\textsuperscript{34,35,41,106,113,129} Although protease inhibitors are thought to have specific antiangiogenic effects, the choice of HAART regimen does not appear to influence protection against epidemic KS.\textsuperscript{6,35,126,130,131}

**Table I.** Post-HAART prognostic criteria in staging epidemic Kaposi sarcoma

<table>
<thead>
<tr>
<th>Prognostic indicators\textsuperscript{a}</th>
<th>Definition\textsuperscript{b}</th>
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<tr>
<td><strong>Tumor extension (T)</strong></td>
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<tr>
<td>T\textsubscript{0} = restriction of lesions to skin and/or lymph nodes and/or minimal oral disease\textsuperscript{c}</td>
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<tr>
<td>T\textsubscript{1} = presence of tumor associated edema or ulceration, extensive oral disease, or visceral involvement</td>
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<tr>
<td><strong>Systemic disease (S)</strong></td>
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<tr>
<td>S\textsubscript{0} = no history of opportunistic infections, “B” symptoms, Karnofsky Performance Status \geq 70</td>
<td></td>
</tr>
<tr>
<td>S\textsubscript{1} = history of opportunistic infections, “B” symptoms, other HIV-related illnesses, Karnofsky Performance Status &lt; 70</td>
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Based on references 1, 34, 42, 121, 122.\textsuperscript{a,b} Initially described by ACTG Oncology Committee for staging AIDS-KS.\textsuperscript{a}Non-nodular solitary Kaposi restricted to palate.\textsuperscript{b}Unexplained fever, night sweats, \geq 10% involuntary weight loss or diarrhea; \geq 2 weeks.

**IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME—ASSOCIATED KS**

In contrast to the general drop in the incidence and severity of AIDS-KS with HAART, some HIV-infected patients are at risk of developing KS within a few weeks of HAART initiation.\textsuperscript{15,34,132} This paradoxical exacerbation of opportunistic infections, such as KS, despite immunologic recovery and favorable virologic response with HAART is known as immune reconstitution inflammatory syndrome (IRIS).\textsuperscript{34} This phenomenon typically affects younger individuals who are profoundly immunosuppressed (CD4 < 100 cells/mm\textsuperscript{3}) at the time of HAART introduction.\textsuperscript{133,134}

IRIS may represent a pathogen-specific immune reconstitution in the presence of a dysregulated hyperinflammatory state and high antigenic burden.\textsuperscript{15} Although acute IRIS occurs in response to a subclinical infection within the first 3 months of HAART initiation, delayed IRIS often develops against antigenic components of dead pathogens anytime after the first 3 months of therapy.\textsuperscript{15,132} To reduce the risk of IRIS, severely immunosuppressed patients naive to therapy should be screened for preexisting opportunistic infections, educated about the potential risk of IRIS with HAART initiation, and monitored closely.\textsuperscript{15,134} The potential risk of IRIS with HAART initiation in patients with advanced immunosuppression supports early institution of antiretroviral therapy to improve CD4 count and reduce viral load.\textsuperscript{135,136} Management of IRIS-associated KS generally does not involve interruption of HAART but may necessitate additional modes of therapy.\textsuperscript{15} Tables II and III, respectively, provide an overview of the management strategies and the spectrum of therapeutic modalities for epidemic Kaposi sarcoma. The 5 drugs currently approved by the Food and Drug Administration (FDA) for treatment of HIV-KS include 0.1% alitretinoin gel for topical therapy and daunorubicin citrate liposome (DNX), pegylated li-
Table II. Potential management strategies for epidemic Kaposi sarcoma based on disease severity

<table>
<thead>
<tr>
<th>Severity of AIDS-KS</th>
<th>Management approach</th>
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<tr>
<td>T&lt;sub&gt;0&lt;/sub&gt;S&lt;sub&gt;0&lt;/sub&gt; (focal disease in the absence of systemic illness)&lt;sup&gt;1,34&lt;/sup&gt;</td>
<td>HAART ± local therapy&lt;sup&gt;1,34&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;0&lt;/sub&gt;S&lt;sub&gt;1&lt;/sub&gt; (early but mildly symptomatic KS, e.g., minimal cutaneous disease)&lt;sup&gt;1,34&lt;/sup&gt;</td>
<td>HAART&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;S&lt;sub&gt;0&lt;/sub&gt; (slowly progressive AIDS-KS)&lt;sup&gt;34&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Extensive disfiguring skin lesions&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Widespread, symptomatic cutaneous AIDS-KS + edema&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Rapidly progressive AIDS-KS&lt;sup&gt;1,34&lt;/sup&gt;</td>
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<tr>
<td>Symptomatic visceral involvement&lt;sup&gt;1,34&lt;/sup&gt;</td>
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<tr>
<td>Obstructive or painful oropharyngeal AIDS-KS&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Inadequate response to HAART alone&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>IRIS-associated KS&lt;sup&gt;34&lt;/sup&gt;</td>
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Based on reference 34. AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome; KS, Kaposi sarcoma.

Table III. Spectrum of therapeutic modalities for epidemic Kaposi sarcoma

<table>
<thead>
<tr>
<th>Local/regional therapy</th>
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<tbody>
<tr>
<td>surgical excision&lt;sup&gt;11,15,137&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>cryotherapy&lt;sup&gt;148&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>sclerotherapy&lt;sup&gt;149,150&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>intralesional vinca-alkaloids, bleomycin&lt;sup&gt;146&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>interferon-alpha&lt;sup&gt;147&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>topical 0.1% altretinoin, imiquimod 5% cream&lt;sup&gt;153&lt;/sup&gt;</td>
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<tr>
<td>radiotherapy&lt;sup&gt;138-141&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>laser therapy&lt;sup&gt;142,143&lt;/sup&gt;</td>
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| Systemic therapy | |
| HAART | |
| NNRT-based therapy<sup>130</sup> | |
| PI-based therapy<sup>130,131</sup> | |

| Chemotherapy | |
| Liposomal anthracyclins<sup>154,155</sup> | |
| Paclitaxel<sup>156</sup> | |
| Oral etoposide<sup>157-159</sup> | |
| Combination agent ABV<sup>154,155,160</sup> or ABVb<sup>159</sup> | |
| Single agent vincristine, vinblastine, vinorelbine, bleomycin<sup>164</sup> | |

| Immune modulators | |
| interferon-alpha 2B<sup>165-167</sup> | |
| Experimental & targeted therapies | |
| Anthrers therapy<sup>166,170</sup> | |
| Angiogenic inhibitors (e.g., thalidomide)<sup>171,172</sup> | |
| VEGF inhibitors<sup>173</sup> | |
| Tyrosine kinase inhibitors<sup>174</sup> | |
| Matrix metalloproteinases<sup>175</sup> | |

| ABV, doxorubicin, bleomycin, vincristine; ABVb, doxorubicin, bleomycin, vinblastine; HAART, highly active antiretroviral therapy; NNRT, non-nucleoside reverse transcriptase; PI, protease inhibitor; VEGF, vascular endothelial growth factor. | |

*Drugs approved by the US Food and Drug Administration for epidemic Kaposi sarcoma.

Table III. Spectrum of therapeutic modalities for epidemic Kaposi sarcoma

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| HAART | |
| NNRT-based therapy<sup>130</sup> | |
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| Immune modulators | |
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*Drugs approved by the US Food and Drug Administration for epidemic Kaposi sarcoma.

Locosomal doxorubicin (PLD), taxane paclitaxel, and interferon alpha-2b for systemic therapy.<sup>33,176,177</sup>

**LOCAL THERAPY**

Local therapy is safe, easy to administer, and efficacious for limited, asymptomatic mucocutaneous lesions of AIDS-KS<sup>1,34,126</sup> It may also be considered when HAART is unavailable, response to HAART is less than optimal, or as a palliative measure in patients with rapidly progressive mucocutaneous lesions causing pain, esthetic concerns, or interference with oral function.<sup>34,36</sup> In addition, local therapy may prevent pain, ulceration, and bleeding in indolent lesions of classic KS.<sup>137</sup> Local delivery of chemotherapeutics to a large, solitary nodular lesion of classic KS may also provide additional benefit to ongoing systemic therapy.<sup>34,126,137</sup>

In spite of these benefits, the local approach is often costly and frequently unsuccessful in controlling the onset of new lesions.<sup>1</sup>

Radiotherapy is highly effective for management of local or regional KS causing pain, bleeding, or edema and remission rates in excess of more than 90% for AIDS-KS have been documented.<sup>1,34,116,138</sup> Radiotherapy has also been effectively used to treat solitary or widespread lesions of classic KS, achieving response rates higher than 80%.<sup>5,11,139</sup> Although generally well-tolerated,<sup>126</sup> potential drawbacks of radiotherapy include risk of radiodermatitis with repeated cutaneous exposure, disease relapse because of radiation-induced fibrosis, and hyperpigmentation.<sup>34,137,178,179</sup> Although oral KS is highly responsive to radiotherapy,<sup>126,179</sup> adverse effects, such as severe mucositis, hyposalivation, and dysguesia have been reported with total doses as low as 7.5 Gy delivered in multiple fractions.<sup>116,178-181</sup> Oral toxicities are often transient and develop early in the course of therapy, necessitating close patient follow-up and institution of palliative measures as needed.<sup>140,179,180</sup> Effective doses range from 8 Gy as a single fraction to 30 Gy delivered over 10 fractions, and it is appropriate to individualize radiotherapy based on a patient’s needs.<sup>125,179,181</sup> Intracavitary contact irradiation—a technique similar to brachytherapy—delivered in 1 or 2 weekly fractions of 5 Gy each through a source introduced into the oral cavity has been reported as effective, well-tolerated, and associated with only minimal mucosal sensitivity.<sup>141</sup> The potential for oral toxicity with external beam radiotherapy together with the
availability of newer therapeutic alternatives support
reserving this modality for limited but symptomatic
or obstructive lesions of the aerodigestive tract.32,179

The focal, superficial mucocutaneous KS is ame-
nable to surgical excision. Potential drawbacks in-
clude functional impairment with repeat procedures
in anatomical areas where tissue is sparse,11,138 as
well as local recurrence of KS.1,11,126,137 In addition,
oral KS is often diffuse or multifocal13 and not
suitable for surgical excision.32,116 The laser ablation
procedure has also proven effective in treating mac-
ular KS affecting the face and oral cavity.142,143

Laser may also be used to treat the surgical bed of
exophytic oral KS after excision to achieve postop-
erative hemostasis.7 Elastic stockings offer another
form of local therapy for KS-associated edema af-
flecting the lower extremities.33

Intralesional injection with vinca alkaloids, such as
vincristine and vinblastine, known to disrupt microtu-
bular function, has been efficacious for local treatment
of mucocutaneous lesions of classic and epidemic
KS.137,144,145 The procedure is painful, there is poten-
tial for necrosis if healthy tissue is injected, and ther-
apeutic effects last about 4 months.1 Therapeutic effi-
cacy for intralesional bleomycin and interferon-alpha
(INF-alpha) in treatment of epidemic and classic KS,
respectively, have also been demonstrated.146,147 Cryo-
therapy with liquid nitrogen for focal skin lesions of
oral KS have been tried, yielding full resolution in
80% of cases, although the procedure may be associ-
ated with local blistering and pain.32,148 Regression of
oral KS with local administration of sodium tetradeyl
sulfate has also been documented.149,150

Retinoid products appear to have an inhibitory
effect on IL-6, a cytokine implicated in KS patho-
genesis, and an antiproliferative effect on KS le-
isons.6 Application of 0.1% alitretinoin gel, the only
self-administered FDA-approved topical agent for
cutaneous AIDS-KS, has shown efficacy for skin
lesions of both classic and HIV-KS.1,34,151,152 Alit-
retinoin gel needs to be applied 2 to 5 times daily as
tolerated and therapeutic response may be delayed by
3 months.1,34 It is also expensive and may be asso-
ciated with skin reactions.1,34 In a study of cutaneous
KS in HIV-seronegative patients, the overall re-
sponse rate to topical 5% imiquimod cream was 47%,
although 53% of subjects experienced local erythema
and pruritis.153 Compared with topical medicaments,
such as alitretinoin or imiquimod, intralesional in-
jections are more efficacious because of faster, more
precise delivery of therapeutic agents;137 however,
the need for the clinician to perform the injections
renders these to be less attractive options.137

**SYSTEMIC CHEMOTHERAPY**

Although early lesions of epidemic KS (T0S0) are
highly responsive to antiretroviral therapy, systemic
chemotherapy is generally indicated for advanced
disease with poor prognostic index.1,34,124,126-128 The
current first-line systemic therapy for advanced,
progressive AIDS-KS includes liposomal anthracy-
clines, including PLD and DNX.1,34,106 PLD has
been equally efficacious as a single agent compared
with multiple agent systemic chemotherapy in man-
agement of AIDS-KS.154,155 In patients with moder-
ate to severe AIDS-KS, the addition of PLD to
HAART led to a significantly better response rate
(76%) compared with HAART alone (20%).127 Li-
posomal formulations have improved the half-
life and toxicity profile relative to anthracyclines
alone.6,35,126 Nevertheless, the response to therapy is
delayed by 3 to 6 months,1 and the main adverse
affects include myelosuppression and opportunistic
infections.1,6,34 Although the potential for these ad-
verse effects is reduced by subcutaneous administra-
tion of granulocyte colony-stimulating factor,34,114
development of anemia and neutropenia after multi-
ple cycles of liposomal agents may necessitate reduc-
tion of dose or cessation of therapy.1 Toxicity rele-
vant to DNX includes stomatitis and infusion
reactions.34

The second-line systemic drug approved by the
FDA for AIDS-KS in patients refractory to or intoler-
ant of liposomal anthracyclines, is paclitaxel.1,34,156
Similar to vinca alkaloids, paclitaxel polymerizes
microtubules and interferes with cell division.34,126
The response rate of advanced AIDS-KS to pacli-
taxel in different studies varies, but is reported as
high as 71%.1,156 Although well tolerated, the intra-
venuous mode of administration and the potential for
bone marrow suppression, peripheral neuropathy, re-
nal dysfunction, alopecia, and arthralgia renders pac-
litaxel a less favorable agent than liposomal antra-
cyclines in the management of widespread KS.34,177

Another second-line drug for progressive AIDS-
KS with incomplete response to liposomal antra-
cyclines is oral etoposide.1 Oral etoposide has been
effective in treatment of both severe classic KS and
advanced AIDS-KS.157-159 Although ideal for self-
administration and less myelosuppressive than vin-
blastine, the risk of alopecia and gastrointestinal
toxicity, as well as the potential for myelosuppres-
sion in up to 60% of those treated, necessitates close
follow-up and limits its application in therapy.1,6,126

Cytotoxic regimens with single or multiple chemother-
apeutic agents for AIDS-KS may be considered when
first- and second-line therapies (liposomal anthracycline
and paclitaxel) are unavailable or failed to resolve the
The first- and second-line agents are expensive and often not readily available in developing countries burdened by the HIV epidemic. The combination regimens, including doxorubicin, bleomycin, and either vincristine or vinblastine (ABV or ABVb) have been widely studied in AIDS-KS with response rate varying from 25% to 88%. The response rate and duration of response in AIDS-KS, as well as reported toxicities to single-agent cytotoxic therapy, such as bleomycin or vinca alkaloids, have also been variable.

Single-agent vincristine is efficacious for AIDS-KS, has a favorable hematological profile, and is generally safe for anemic and neutropenic patients. The potential risk for neurotoxicity, however, requires exclusion of patients concomitantly treated with specific antiretroviral drugs, as well as those with preexisting neuropathy. In addition, patients should be screened for neuropathy at each visit. Systemic vinblastine alone was found effective in 25% of AIDS-KS cases treated, providing remission for nearly 4 months. Although less neurotoxic than vincristine, the risk of myelosuppression is a concern with systemic administration of vinblastine. In a study by Nasti et al., efficacy in treatment of AIDS-KS was also achieved with vinorelbine, also a vinca alkaloid. Vinorelbine has mild and reversible adverse effects and is effective in treating AIDS-KS refractory to regimens containing either vinblastine or vincristine. The response rate of AIDS-KS to single-agent chemotherapy with bleomycin is also variable depending on dosing and route of administration.

INF-alpha, an immunomodulatory agent with antiviral and antiangiogenic properties, has dose-dependent efficacy in treatment of AIDS-KS when administered systemically. This is particularly evident in patients with relatively preserved immune function, lacking lymphomalike “B” symptoms and those with exclusively skin lesions. Concurrent antiretroviral therapy with a lower dose of INF-alpha appear to provide similar therapeutic outcome for AIDS-KS with less toxicity. The delayed therapeutic response renders INF-alpha inappropriate for treatment of rapidly progressive or symptomatic visceral KS.

To improve efficacy and overcome chemotherapya-associated toxicity, new therapeutic approaches have focused on direct control of KSHV for prevention and treatment of KS. Anti-herpes medications were shown to reduce plasma viral load of KSHV and prevent KS in KSHV-seropositive transplant recipients. Anti-herpes drugs ganciclovir and foscarnet were found to reduce the risk of KS by up to 62% among HIV-positive subjects. Moreover, a decrease in mucosal replication of KSHV with valganciclovir has been demonstrated. Although limited efficacy does not support the use of anti-herpes drugs alone, the combination of anti-herpes medications with HAART offers the promise to diminish replication of both viruses, prevent new lesions, and help regress lesions already present. Other efforts have focused on developing novel inhibitors to target angiogenesis, VEGF, tyrosine kinase, and matrix metalloproteinases, all of which appear to play a role in KS pathogenesis.

ROLE OF THE ORAL HEALTH CARE PROVIDER

All forms of KS may manifest in the oral cavity, and KSHV appears essential to development of all clinical variants. Although not clearly understood, oropharyngeal epithelial cells may harbor KSHV, facilitating its replication and transmission through saliva. Oral health care practitioners should be familiar with orofacial manifestations of KS, contribute to prevention of KS by educating patients about risk factors, and question those engaged in risk behaviors about the presence of mucocutaneous lesions. Manifestation of KS in the oral cavity may indicate further deterioration of the immune system or signal development of IRIS following the start of antiretroviral therapy. In an untreated HIV patient, diagnosis of oral KS is also considered a significant prognostic marker of survival. In addition, the onset of oral KS may be the first sign of undiagnosed HIV infection. Therefore, oral lesions clinically suggestive of KS should be biopsied and patients with biopsy-proven KS should be tested for HIV. Development of KS in the oral cavity may cause local tissue damage, pain, bleeding, or interference with oral functions and prosthesis wear, all of which may negatively affect a patient’s nutritional status, adherence to medical therapy, and quality of life. Close communication between an oral health care provider and the patient’s infectious disease specialist facilitates a mutual understanding of the extent of KS spread, severity of symptoms, available therapeutic strategies, and potential adverse effects of therapy. Oral health care providers may contribute to interdisciplinary management of oral KS by using a variety of local measures, such as surgical excision, laser ablation, and intralesional injections to improve local control and systemic therapy.
help accessible oral lesions regress in size, and to provide palliation.

REFERENCES


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