Invited Review

# A Review of Human Herpesvirus 8, the Kaposi's Sarcoma-Associated Herpesvirus, in the Pediatric Population

**Dorothy E. Dow,[1,2] Coleen K. Cunningham,[1] and Ann M. Buchanan[1,2,3]**
[1]Division of Infectious Diseases, Department of Pediatrics, Duke University Medical Center, Durham, North Carolina; [2]Kilimanjaro Christian Medical Centre, Moshi, Tanzania; and [3]Duke Global Health Institute, Duke University, Durham, North Carolina

**Corresponding Author:** Dorothy Dow, MD, MScGH, Fellow, Pediatric Infectious Diseases, Duke University, DUMC 3499, Durham, NC 27710. E-mail: dorothy.dow@duke.edu.

Received April 9, 2013; revisions received June 20, 2013; accepted June 27, 2013; electronically published September 4, 2013.

Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma (KS)–associated herpesvirus, is the etiologic agent responsible for all types of KS. Although the majority of pediatric KS cases occur in sub-Saharan Africa, a rise in pediatric transplant KS has been reported in developed countries. In addition, HHV-8 is increasingly described as an infectious cause of hemophagocytic lymphohistiocytosis in children. Transmission of HHV-8 among children is poorly understood; however, the literature strongly suggests that horizontal transmission plays a critical role. Acute infection with HHV-8 and progression to KS in children may be different than in adults, and diagnosis may be overlooked. Currently, neither adult nor pediatric treatment guidelines exist. This review provides an overview of HHV-8 disease in children as it relates to epidemic KS, transplant KS, and other disease manifestations. The current state of the literature is reviewed and knowledge gaps are identified for future exploration.

**Key words.** children; HHV-8; HIV; Kaposi's sarcoma; KSHV.

## BACKGROUND

Kaposi's sarcoma (KS) was first described in 1872 by Moritz Kaposi [1, 2]. It was originally thought to be a tumor exclusive to elderly men of Mediterranean or Jewish descent, but by the 1950s it was also recognized in parts of sub-Saharan Africa. Kaposi's sarcoma gained heightened awareness with the beginning of the acquired immune deficiency syndrome (AIDS) epidemic when young, primarily homosexual men across the United States, suddenly presented with an aggressive and disseminated form of KS, now termed epidemic KS [3]. The escalation in cases of KS brought increased attention to this vascular tumor and an urgency to discover the etiologic agent and risk factors leading to KS disease.

In 1994, Chang et al [4] discovered human herpesvirus 8 (HHV-8). It is also known as KS-associated herpesvirus (KSHV) and is the etiologic agent responsible for all types of KS as well as primary effusion B-cell lymphoma and most forms of the lymphoproliferative disorder multicentric Castleman's disease. A description of the 4 different types of KS is as follows and can be found in Table 1: classical, endemic, iatrogenic/transplant, and AIDS-associated/epidemic KS. As with other oncogenic viruses, HHV-8 is a necessary but insufficient cause of malignancy [5]. Seropositivity alone does not predict progression to KS or other diseases. Human immunodeficiency virus (HIV) infection and immunodeficiency are major risk factors, although the exact triggers that enable HHV-8 to progress to KS remain unknown.

## EPIDEMIOLOGY

Human herpesvirus 8 seroprevalence varies widely throughout the world. Geographic areas are often categorized into 3 groups: low HHV-8 seroprevalence (<5%) traditionally found in North America, much of Europe, and Asia; intermediate seroprevalence (5%–20%), which includes the Mediterranean, Eastern Europe, Caribbean, and Middle East; and high seroprevalence (>50%), which includes much of Africa and regions of the Brazilian Amazon [6-8].

Comparing HHV-8 infection rates across studies can be difficult because there is no true gold standard for diagnosis. Although traditionally seroprevalence is thought to be

Journal of the Pediatric Infectious Diseases Society, Vol. 3, No. 1, pp. 66–76, 2014. DOI:10.1093/jpids/pit051
© The Author 2013. Published by Oxford University Press on behalf of the Pediatric Infectious Diseases Society.
All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

**Table 1.** Four Types of Kaposi's Sarcoma

| Type of KS | Characteristics | | |
|---|---|---|---|
| | Geographic | Population | Clinical Presentation |
| Classic or Sporadic | Mediterranean, Eastern European | Elderly men | Indolent, cutaneous lesions |
| Endemic or African | Equatorial Africa | Predominantly men (immunocompetent) | Often lymphatic involvement of the feet and legs with lymphoedema and nodular cutaneous plaques |
| Transplant or Iatrogenic | More frequent in developed world setting | Immunosuppressive therapy, organ transplant | Aggressive; often involving mucosa, gingival hyperplasia, or visceral organs; sometimes without cutaneous manifestation |
| Epidemic or AIDS- associated | Worldwide | HIV-infected | Various, more aggressive course, IRIS |

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; KS, Kaposi's sarcoma.

low among children in North America, 1 study of 123 otherwise healthy children ages 4–13 years attending routine pediatric care in South Texas demonstrated a HHV-8 seroprevalence of 26% [9]. The Reaching for Excellence in Adolescent Care and Health (REACH) study evaluated youth ages 13–18 years who were at high risk for HIV or were already infected with HIV. The study demonstrated that 11.2% of enrolled youth were HHV-8 antibody positive with no statistically significant difference between those with and without HIV infection [10]. These studies demonstrate a higher than expected seroprevalence for children in select populations living in the United States.

Numerous studies evaluating HHV-8 seroprevalence throughout Africa demonstrate that the majority of children develop HHV-8 antibodies between 1 and 13 years of age [11–15]. The higher seroprevalence of HHV-8 in Africa suggests that either the virus has been present on the continent much longer, or there is a yet unknown cofactor that dramatically increases the efficiency of HHV-8 transmission [15]. In spite of its prevalence in Africa, few who are infected go on to develop KS.

The "KS belt" is a region in equatorial Africa where even before HIV, the progression of HHV-8 to endemic KS was particularly high [16]. The belt extends from the coast of Cameroon through northeast Democratic Republic of Congo and down the Rift Valley to Malawi including Uganda, Tanzania, and Zambia [17]. In this area, KS is among the most common pediatric cancers, often second only to Burkitt's lymphoma [18, 19].

Environmental cofactors such as volcanic soil (rich in alumino-silicates) were once thought to play a role in progression to KS in these endemic regions [20]. Regional plant exposure has also been proposed to influence HHV-8 progression by reactivating latent virus [21]. Coinfections with certain insects, helminthic, or parasitic infections, including malaria have been considered [5, 14, 22, 23], as well as the "promoter arthropod hypothesis," which suggests that arthropod bites are an indirect cofactor when mothers infected with HHV-8 use their saliva to alleviate pruritis from their child's bite, thereby transmitting the virus [23, 24]. Each of these cofactors has been hypothesized to influence KS progression, although to date none have been proven.

**Impact of HIV**

The impact of HIV on HHV-8 disease has been enormous, suggesting that HIV provides a necessary cofactor for progression from HHV-8 infection to KS [11, 14, 15, 25]. Data from Children's Cancer Registries in South Africa [26], Zimbabwe [27], and Uganda [28] demonstrate a 30- to 40-fold increase in pediatric KS since 1987. In Zambia, nearly 20% of childhood cancers between 1987 and 1992 were KS compared to only 6% before 1986; nearly 60% of these KS tumors occurred in children under 5 years of age [29].

With the introduction of highly active antiretroviral therapy (HAART), HIV is treated earlier and more effectively, and in developed countries epidemic KS cases are on the decline [30, 31]. Globally, however, ART coverage is estimated to reach only 28% of qualifying children (57% of qualifying adults), and, despite improved ART distribution, sub-Saharan Africa has yet to demonstrate the same decline in epidemic KS [32, 33]. In addition, in countries with longstanding access to ART, approximately one-third of HIV-infected people presenting with KS are receiving HAART and have fully suppressed HIV and CD4 counts >200 cells/μL [34, 35]. Reasons for KS disease in HAART-treated individuals remain unclear because immunodeficiency is thought to play a key role in pathogenesis. Perhaps the presence of HIV, even at low levels, is enough to induce HHV-8 to manifest KS lesions, but it remains critically important to better understand the HIV/HHV-8 interaction and the triggers that stimulate progression to KS.

## VIROLOGY AND PATHOGENESIS

Human herpesvirus 8 is the latest addition to the human herpesvirus family. Like Epstein-Barr virus (EBV), HHV-8 is a DNA, gammaherpesvirus. Human herpesvirus 8 is capable of infecting several cell types including monocytes, dendritic cells, B lymphocytes, oral epithelial cells, and, in KS tumors, endothelial cells. The virus exists in both lytic and latent forms. Viral pathogenesis of KS depends upon regulation between these 2 phases.

The lytic phase is necessary for primary infection of a new host. After primary infection, virus persists in the latent phase with episomal DNA expressing only a few gene products from 4 open reading frames (ORFs) including v-FLIP, v-cyclin, Kaposins A, B, C, and most notably latent nuclear antigen (LANA-1) encoded by ORF-73 [36–38]. Latent phase virus can be induced to reenter the lytic state of viral replication, although triggers for this phase transition are not fully elucidated. Clinical disease is typically due to chronic infection, but the relative importance of lytic reactivation and replication from latency remains controversial. In some cases, especially organ transplant, disease can manifest from primary disseminated lytic infection [39].

In the latent phase, lytic proteins are suppressed; however, activation of ORF-50 encodes the replication and transcription factor activator that expresses lytic cycle activation genes capable of stimulating the complete lytic cycle [37, 38, 40]. Recent studies demonstrate HHV-8-encoded microRNA [40] and tousled-like kinases [41] may play an important role in controlling cellular reactivation from latency via ORF-50. Alternative mechanisms that may activate viral ORF-50 include oxidative stress and hypoxia via the molecule $H_2O_2$ [42], proinflammatory cytokines such as interferon gamma [43], and proangiogenic cytokines [44]. The HIV-1 transactivator protein (Tat) is also hypothesized to contribute to this interplay, although additional, as yet unknown factors may also be required to complete the HHV-8 lytic transformation and progression to KS [45, 46].

## TRANSMISSION

### Horizontal

Human herpesvirus 8 transmission remains an area of investigation. With the discovery of HHV-8 and the rise of KS among men who have sex with men, HHV-8 was presumed to be a sexually transmitted virus [47]. This was supported by the demonstration of HHV-8 DNA in semen [48]. A study evaluating sites of HHV-8 shedding, however, also found virus in vaginal (2.3%) and cervical (4%) secretions, but prevalence was highest in saliva (32%) and mouth swabs (28%), demonstrating oral mucosa to be a primary site of viral shedding [49]. The high seroprevalence in African children also suggests that transmission likely occurs via salivary exchange, similar to that seen in EBV [50]. Transmission likely occurs within families, and infection is highest among children whose mother, first-degree relative, or next-older sibling is also seropositive [8, 13, 51–53]. In Uganda, childhood exposure to premasticated food (only 8.8% of participants) was not found to be a risk factor, although sharing plates (91% of participants) was associated with risk [11]. Low socioeconomic status was a contributing risk that may reflect more crowded and less hygienic living conditions as seen in childhood transmission of other oncogenic viruses such as EBV and hepatitis B [6, 15, 54, 55]. There is no evidence for fecal-oral transmission [54].

### Vertical

Although horizontal transmission of HHV-8 is well described, few studies have evaluated the overall risk of vertical and breast milk transmission. In a prospective cohort study in Zambia, among 89 HHV-8 seropositive mothers (2% with active KS lesions and 36% coinfected with HIV), 15% had detectable HHV-8 DNA in blood and 2 (2%) infants (both born to HIV-negative mothers) had blood samples positive for HHV-8 DNA in the first 24 hours of life [56]. Another study from Burkina Faso demonstrated that of 107 HIV-positive pregnant women receiving a highly efficacious prevention of mother-to-child transmission regimen (zidovudine, lamivudine, nevirapine), 12% were coinfected with HHV-8, and there was no vertical transmission of either virus [57].

Just as cytomegalovirus (CMV; HHV-5) can be transmitted via breast milk, studies have investigated the presence of HHV-8 in breast milk. A South African study demonstrated HHV-8 DNA in 12 of 43 participants' breast milk samples among seropositive mothers with high lytic HHV-8 antibody titers [13]. In contrast, HHV-8 was not found in breast milk of 2 separate cohorts of HHV-8 seropositive, postpartum women from Zambia and Zimbabwe [58, 59]. These studies show that although vertical and breast milk transmission of HHV-8 may be possible, it seems a rare event.

### Blood Transfusion

Research is ongoing to establish transmission risk from blood transfusion. A study of 991 HHV-8 seronegative children (age 0.1–4.6 years) from Uganda demonstrates

that those who received HHV-8 seropositive blood (43%) had a significant, 2.8% excess risk of seroconverting 3–10 weeks after transfusion [60]. Recently, this same research group evaluated the mortality risk of the pediatric cohort and demonstrated a statistically significant 2-fold increased risk of death after transfusion with HHV-8-positive short-stored blood (<4 days) compared with either HHV-8-negative or HHV-8-positive, long-stored blood (≥4 days) [61]. Results from these studies suggest that primary HHV-8 infection does occur after blood transfusion and that HHV-8-positive, short-stored blood might be associated with higher mortality [61].

## CLINICAL MANIFESTATIONS

### Primary Infection

Clinical manifestations of acute HHV-8 infection vary based on immune status at the time of primary infection. Studies from young children between 6 months and 3 years of age in both Egypt and Zambia suggest that although immunocompetent children may remain asymptomatic with primary infection, fever, rash, and upper respiratory tract symptoms are common, albeit nonspecific manifestations [51, 62, 63]. Among immunocompromised patients, primary infection may present with lymphadenopathy, acute pancytopenia, and rapid progression to disseminated disease [64].

### Epidemic KS

Development of epidemic KS typically presents as 1 or a combination of cutaneous, lymphadenopathic, or visceral manifestations. Epidemic KS in children commonly involves the lymphatic system and results in a more aggressive clinical course compared with the cutaneous and mucosal presentation commonly seen in adults [18, 19, 26, 28, 39, 65, 66]. Children who acquire HIV via perinatal or breastfeeding transmission are at risk for subsequent HHV-8 infection, and the sequence of viral acquisition may play a role in disease progression. In 2 prospective studies, men who have sex with men who acquired HHV-8 infection after infection with HIV demonstrated a significantly greater risk and faster progression to KS [67, 68]. Whether the sequence of acquisition of these 2 viral infections or inherent differences in childhood response to infection play a role in disease presentation requires further study.

Cutaneous KS lesions tend to follow the "Koebner phenomenon" with lesions appearing in areas of prior infection or injury, further suggesting that an inflammatory microenvironment may promote KS formation [28, 30]. Cutaneous lesions of KS are rarely painful or pruritic and appear as hues of purple and pink, which differ in appearance depending on the patients' skin pigmentation and racial background. Cutaneous KS lesions can mimic other disease processes such as purpura, hematoma, tinea corporis, and bacillary angiomatosis, and a high clinical index of suspicion must be maintained for accurate diagnosis.

Extracutaneous spread of KS is common. Oral mucosa, most frequently on the palate or gingiva, may become friable, bleed, and make it difficult to eat. Visceral lesions can occur with or without cutaneous lesions and can appear in just about any organ, although gastrointestinal and pulmonary sites are most common. Symptoms involving the gastrointestinal tract may include melena, hematemesis, or hematochezia. Ramdial et al [69] report a case series of 6 pediatric patients with AIDS-associated KS intussusception presenting with emesis and fever with no cutaneous lesions. Pulmonary involvement may also present without skin disease as demonstrated in approximately 5%–23% of adult KS patients who present with isolated pulmonary symptoms such as nonproductive cough, hemoptysis, dyspnea, pain, and fever [70]. Such pulmonary disease can mimic other opportunistic infections such as tuberculosis, pneumonia, and other malignant processes.

### Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) may occur soon after an HIV-positive patient begins HAART in the presence of an underlying infection, including KS (IRIS-KS). Currently, there is no specific case definition for IRIS-KS, but broad clinical criteria for IRIS are generally applied (Table 2) [71].

Little data exist to define risk factors for IRIS-KS, and to date no pediatric studies have evaluated the question. Unlike IRIS associated with tuberculosis and other opportunistic infections, IRIS-KS is not predicted by low CD4 count [72, 73]. An adult study from Mozambique identified IRIS-KS in 8 of 69 (12%) adults initiating HAART and found that clinically identified KS lesions before starting therapy, high plasma HHV-8 DNA, high HIV-1 RNA, or anemia were risk factors for the development of IRIS-KS [73]. A prospective Ugandan study using a much broader IRIS-KS definition found 57% (17 of 30) of the adult cohort initiating HAART had IRIS-KS; however, all but 3 cases spontaneously resolved while continuing on HAART [74]. A recent, retrospective pediatric cohort with epidemic KS in Botswana and Malawi identified 18 of 81 patients (22%) as having IRIS-KS [75]. This result is in contrast to a pediatric KS cohort from Mozambique that found no cases [76].

### Iatrogenic/Transplant KS

The clinical spectrum of HHV-8 infection and progression to KS in the pediatric transplant population is not yet fully elucidated [77]. Risk of developing KS after

**Table 2.** Immune Reconstitution Inflammatory Syndrome-Kaposi's Sarcoma

| Classification Criteria | |
|---|---|
| Major (only 1 required) | (1) Abrupt, paradoxical clinical worsening of previously existing KS with immune system restoration and viral load suppression |
| | (2) Unmasking a new presentation of previously unknown KS |
| Minor (2 of 3 required) | (1) Rise in CD4+ T cell count after starting ART |
| | (2) Exaggerated immune response to KS |
| | (3) Spontaneous resolution of KS without specific chemotherapy while continuing ART |

Abbreviations: ART, antiretroviral therapy; KS, Kaposi's sarcoma.

transplant is 1000-fold greater than in age-matched controls not receiving a transplant, with an overall reported risk of 0.4%–6% among all solid-organ transplant recipients depending on baseline seroprevalence and geographical region [77]. Pediatric patients post-liver transplant who develop KS may face a dismal prognosis [78, 79]. Celtik et al [78] describes a 15-month-old child who underwent liver transplant with subsequent pancytopenia, lymphadenopathy, edema, and subconjunctival bleeding. Serology for CMV and EBV were negative, but a cervical node biopsy confirmed the diagnosis of disseminated KS [78]. Similar findings of multivisceral KS after pediatric liver transplant have also been described in Mexico, France, and Turkey; many with fatal outcomes [79-81]. Likewise, HHV-8 progression to KS disease has been described after bone marrow transplant in children [82–84], including an 8-year-old presenting with gingival hypertrophy and cutaneous and respiratory tract lesions after allogenic hematopoietic stem cell transplantation [85]. Cases have been described in adults post-lung transplant [86] and frequently after renal transplant [87].

**Other Pediatric Manifestations**

In addition to KS, HHV-8 should be considered a potential trigger for hemophagocytic lymphohistiocytosis in children. Case studies have described this complication in 2 of 3 triplet infants without HIV infection [88], in HIV-positive patients with known KS [89], and in a 2.5-year-old boy with X-linked lymphoproliferative phenotype [90]. Patients with primary immune deficiency may also be at risk for disseminated HHV-8 infection, as has been reported with a fatal outcome in a young patient with DiGeorge syndrome [91].

## DIAGNOSIS

To diagnose infection, seropositivity is commonly determined using both (1) an enzyme-linked immunosorbent assay to detect lytic proteins usually from ORF-65 and recombinant K8.1 proteins and/or (2) an immunofluorescence assay to detect LANA protein produced by ORF-73 and/or other lytic antigens. Studies vary in algorithm and cutoff values to define whether lytic, latent, or both antibody types are required for a sample to be deemed positive. In general, these assays have a reported sensitivity and specificity ranging from 50% to 95% [13, 15, 92–94].

Molecular studies are also available, although not commonly used. Standard polymerase chain reaction can detect virus in both lytic and latent state, but it does not differentiate between the two. Human herpesvirus 8 copy number can be low and virus can be sporadically detected in tissue and blood [95]. Detection of HHV-8 viremia in an HIV-positive person is a risk factor for progression to KS disease [96, 97]. Recently, HHV-8 mRNA was used to investigate new cases of epidemic KS in patients with fully suppressed HIV and stable CD4 >200 cells/mL. Tumor cells were classified as having lytic viral mRNA (detectable mRNA levels for $\geq$50% of viral genes) or tightly latent virus expressing few gene products as seen in recent cases of epidemic KS with suppressed HIV [34]. Research is ongoing to understand the transformation of HHV-8 to epidemic KS in both immunosuppressed patients with high HIV viral load as well as those patients with suppressed HIV who progress to KS despite excellent immune response to HAART.

Clinical recognition of cutaneous or mucosal lesions remains a critical step in diagnosing KS; however, biopsy with histologic diagnosis is the gold standard and should be obtained when available [98]. The histologic hallmark of KS is spindle-shaped cells of endothelial origin with slit-like blood vessels and peripheral inflammatory cells. Lesions are classified as patch (earliest foci of KS lesions), plaque (more indurated, edematous, and violaceous), or nodal (visible mass dominated by spindle cells) stages [34, 99].

Visceral involvement can occur with or without cutaneous lesions. The gastrointestinal tract can be assessed for fecal occult blood and ultrasound, radiographic imaging, or endoscopy. Pulmonary involvement may not be visible or may be difficult to distinguish from other disease processes on chest radiographs. Lesions in the bronchial tree below the carina are suggestive of pulmonary involvement in a patient suspected to have KS [70]. Chest radiograph may demonstrate reticular opacities and parenchymal

nodules with a bronchovascular distribution and can reveal hilar or mediastinal adenopathy, pleural effusion, or consolidation [70]. Diagnosis may require bronchoscopy with biopsy.

### Classification and Prognosis

Several cancer staging systems have been established to describe disease severity and prognosis. The most frequently used classification was proposed by the AIDS Clinical Trials Group (ACTG) in 1988 and validated by Krown et al [100]. It classifies AIDS-associated KS patients into good or poor risk categories based on the following criteria: tumor extent (T), immune system via CD4 count (I), and HIV-related systemic illness (S) (Table 3).

These criteria were reevaluated in the post-HAART era with T and S staging continuing to offer significant prognostic value [101, 102]. Poor prognosis was demonstrated with adult patients stage T1/S1 (3-year survival of 53%), and those with pulmonary involvement had the poorest prognosis. Patients with any other stage (T0/S1, T1/S0, T0/S0) exhibited 80% or greater survival at 3 years [102]. Published pediatric staging data have been primarily assigned retrospectively and similarly suggest a poor prognosis with palatal or visceral involvement [26] and T1/S1 staging [76]. In contrast, a recent pediatric study found that only the degree of immunosuppression was associated with mortality [75]. Prospective staging data in pediatrics are needed to further understand prognostic predictors among children.

## TREATMENT

### Kaposi's Sarcoma

Currently, there are no established therapeutic guidelines for KS, and most treatment studies are retrospective with few options available in resource-limited settings [85, 103]. For focal disease, local therapy such as intralesional chemotherapy (vinblastine) or topical alitretinoin can be used for palliation or aesthetic purposes [103]. Radiation therapy can be used to treat larger volume disease that does not require systemic chemotherapy, but it is painful and side effects can last for several weeks [87, 103].

### Epidemic KS in Resource-Limited Settings

For treatment of AIDS-associated KS, HAART is first-line therapy, and the Pediatric Management and Treatment of Opportunistic Guidelines recommend starting HAART in KS patients as soon as possible [104]. Although protease inhibitors (PIs) demonstrate antiangiogenic and antitumor activity in vitro, published literature is limited to observational studies, and no prospective, adequately powered clinical trials have compared initiation of PI versus nonnucleoside reverse transcriptase inhibitor regimens for treatment in AIDS-KS patients [26, 105]. Although definitive clinical evidence for benefit is lacking, many experts use PIs as first line for patients with AIDS-KS [106], and PIs are being investigated for use in other cancers as well [107, 108].

Treatment recommendations of epidemic KS in children are limited to retrospective studies across sub-Saharan Africa. A retrospective review of 70 pediatric epidemic KS cases in South Africa demonstrated 53% mortality within an average of 4 months after presentation. In this study, survival correlated with initiation of HAART. Chemotherapy was administered in a variety of combinations of bleomycin, doxorubicin, and vincristine, but it did not afford statistically significant survival benefit [26]. A Ugandan study evaluated 73 children with epidemic KS for which only 32 had outcome data available. Of these 32 patients, 20 (62.5%) had complete resolution of their KS, the majority of whom received combinations of HAART and chemotherapy (vincristine or bleomycin) [19]. In Botswana and Malawi, 69 of 81 children with epidemic KS had follow-up data at 12 months and demonstrated mortality of 57%. Among the survivors, 7 children received HAART alone (50% survival in the HAART only group) and 23 received HAART plus a combination of chemotherapy (vincristine, bleomycin, and doxorubicin), with 64% survival in this HAART plus chemotherapy group [75]. A retrospective study of 32 pediatric patients with biopsy-proven KS from Mozambique demonstrated that of 24 patients who received a combination of HAART and paclitaxel, all had complete resolution by 10 months after treatment, although 3 had subsequent relapse [76].

**Table 3.** Original AIDS Clinical Trials Group/Krown Tumor Staging [100]

| Tumor Extent (T) | Immune System (I) | Systemic Illness (S) |
|---|---|---|
| T0: Lesion confined to skin +/– lymph node involvement | I0: CD4 > 200 cells/mL | S0: Opportunistic infections without B symptoms[a] |
| T1: Tumor associated edema, ulceration, extensive oral KS, or visceral involvement | I1: CD4 < 200 cells/mL[b] | S1: Opportunistic infections with B symptoms or Karnofsky score <70 |

Abbreviations: AIDS, acquired immune deficiency syndrome; HAART, highly active antiretroviral therapy; KS, Kaposi's sarcoma.

[a]B symptoms include the following: fever, night sweats, weight loss.

[b]Revised down to CD4 ≤ 150 cells/mL [101] and CD4 < 100 cells/mL [102] and ultimately not found to offer significant prognostic value in the post-HAART era.

These studies lacked well documented staging criteria and important demographic, clinical, and follow-up data. To date, there have been no prospective studies in pediatrics; therefore, therapeutic options are extrapolated from the adult literature [109]. Data suggest that patients with favorable risk (T0 stage) may fully respond to HAART alone. Adjunctive chemotherapy in rapidly progressive KS with poor prognosis or visceral involvement appears justified [26, 110]; however, initiation of HAART should not be delayed to deliver chemotherapy [104].

A Cochrane review to evaluate high-quality therapeutic randomized control trials in epidemic KS relevant to resource-poor settings concluded that of 5 trials meeting inclusion criteria, only radiotherapy for cutaneous lesions is likely to be available in a resource-poor setting. This review suggests a search for a chemotherapeutic agent to treat epidemic KS in resource-poor settings among patients who are already on HAART should be made a priority [103].

Most chemotherapeutic trials have taken place in the United States of America or Europe. Liposomal doxorubicin and paclitaxel have been identified as good therapeutic options, although neither is widely available in the developing world [103, 111]. A prospective, randomized control trial from South Africa evaluated AIDS-associated KS in adults, stratified by ACTG staging criteria, and demonstrated that chemotherapy (vincristine, bleomycin, and doxorubicin or oral etoposide) in addition to HAART afforded a 27% increased response rate, but it did not improve survival outcomes compared with HAART alone [111].

Antiherpetic viral therapy has been evaluated for prevention and considered for potential treatment of KS. Randomized, placebo-controlled trials have demonstrated that ganciclovir significantly reduced the incident risk of KS [112], and valganciclovir significantly decreased oropharyngeal shedding of HHV-8 by 46% [113]. Lesions that express lytic proteins, such as viral thymidine kinase or phosphorylase, may be susceptible to antiviral treatment, but the majority of lesions in epidemic KS are found in the latent state [34, 42]. These studies suggest evidence for antiviral therapy for prevention; however, evidence for use of antiviral drugs against HHV-8 for KS treatment is lacking. Targeting HHV-8 replication requires further study to present a potential strategy for the prevention and perhaps treatment of KS [108].

### Iatrogenic/Transplant KS

Several different strategies have aimed to treat transplant-related KS, but optimal therapy remains unknown. The most common approach to treatment involves reduction of immunosuppression and substitution of commonly used immunosuppressive agents such as tacrolimus for sirolimus (mammalian target of rapamycin inhibitor) due to its antitumorogenic properties [80, 87]. Use of paclitaxel, a mitotic inhibitor, has been successful in advanced forms of iatrogenic KS [78, 114]. Prostaglandin $E_2$ inhibitors are being investigated [99], as are new interventions targeting paracrine and autocrine cytokines involved in transformation of infected cells [115]. Antioxidants and anti-inflammatory drugs are also being explored as preventive or therapeutic options [42]. Use of Toll-like receptor-4 agonists have been proposed to boost innate immunity and control KSHV infection, although to date no human trials have been conducted [116]. A summary of treatment recommendations can be found in Table 4.

**Table 4.** Management Summary of HHV-8 Disease

| Phenotype | Treatment | |
|---|---|---|
| Acute (primary) infection | Immunocompetent | Supportive care |
| | Immunosuppressed | Consider antiviral therapy<br>• Ganciclovir<br>• Valganciclovir |
| Epidemic KS | Local disease (T0) | HAART<br>Intralesional chemotherapy<br>• Vinblastine<br>• Topical alitretinoin<br>Radiation Therapy |
| | Disseminated disease (T1) | HAART<br>Chemotherapy (as available)<br>• Vincristine, bleomycin, doxorubicin<br>• Etoposide<br>• Paclitaxel<br>• Liposomal doxorubicin |
| | Potential prevention | Antiviral therapy<br>• Ganciclovir<br>• Valganciclovir |
| Transplant KS | | Reduce immunosuppression<br>Use a mTOR inhibitor<br>• Sirolimus (Rapamycin)[a]<br>Paclitaxel |

Abbreviations: HAART, highly active antiretroviral therapy; HHV-8, human herpesvirus 8; KS, Kaposi's sarcoma; mTOR, mammalian target of rapamycin; T, tumor extent.

[a]Use mTOR inhibitors with caution in liver transplant patients due to concern for hepatic artery thrombosis.

## CONCLUSIONS

Children with KS are a vulnerable population with few data to guide best medical practice. These children suffer significant pain, tumor-associated edema, and aesthetically displeasing appearance leading to stigma. They suffer from this disease emotionally and physically, and unfortunately many suffer fatal consequences.

The impact of epidemic KS in children living in sub-Saharan Africa is substantial. Severe cases are a continual dilemma, and, although HAART has brought tremendous treatment benefit, a majority of pediatric patients are not receiving treatment. Acquired immune deficiency syndrome-related malignancies are now a priority area, and KS in the pediatric population should not be an exception. In addition, the burgeoning field of pediatric transplant has brought an increase in transplant-KS with more children suffering from this form of disease. Triggers for progression of HHV-8 to KS disease and best treatment practices remain unknown. Outcome data for pediatric patients with KS are poorly documented and retrospective in nature. Lack of prospective data leaves major knowledge gaps, and targeted research is necessary to better understand viral transmission, progression to KS, and approaches to therapy in children. Clinicians must remain aware of the manifestations of HHV-8 in children and maintain a high clinical suspicion, especially in pediatric transplant and HIV medicine.

**Acknowledgments**

We sincerely thank Dr Micah Luftig (Associate Professor and Deputy Director of the Center for Virology at Duke University Medical Center) for his thoughtful critique and advice regarding this HHV-8 topical review.

***Financial support.*** This review was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development training grant to the Division of Infectious Diseases, Department of Pediatrics, Duke University Medical Center (T32 HD060558; to D. E. D.) and by the Duke Center for AIDS Research, a National Institutes of Health-funded program (5P30 AI064518; to C. K. C. and A. M. B.).

***Potential conflicts of interest.*** All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**

1. Braun M. Classics in oncology. Idiopathic multiple pigmented sarcoma of the skin by Kaposi. CA Cancer J Clin **1982**; 32: 340–7.
2. Kaposi M. Idiopathisches multiples Pigmentsarkom der Haut. Arch Dermatol Syph (Prague) **1872**; 4:265–73.
3. Hymes KB, Cheung T, Greene JB, et al. Kaposi's sarcoma in homosexual men-a report of eight cases. Lancet **1981**; 2: 598–600.
4. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science **1994**; 266:1865–9.
5. Pfeiffer RM, Wheeler WA, Mbisa G, et al. Geographic heterogeneity of prevalence of the human herpesvirus 8 in sub-Saharan Africa: clues about etiology. Ann Epidemiol **2010**; 20:958–63.
6. Caterino-de-Araujo A, Manuel RC, Del Bianco R, et al. Seroprevalence of human herpesvirus 8 infection in individuals from health care centers in Mozambique: potential for endemic and epidemic Kaposi's sarcoma. J Med Virol **2010**; 82: 1216–23.
7. Chatlynne LG, Ablashi DV. Seroepidemiology of Kaposi's sarcoma-associated herpesvirus (KSHV). Semin Cancer Biol **1999**; 9:175–85.
8. Mbulaiteye SM, Pfeiffer RM, Whitby D, et al. Human herpesvirus 8 infection within families in rural Tanzania. J Infect Dis **2003**; 187:1780–5.
9. Baillargeon J, Leach CT, Deng JH, et al. High prevalence of human herpesvirus 8 (HHV-8) infection in south Texas children. J Med Virol **2002**; 67:542–8.
10. Casper C, Meier AS, Wald A, et al. Human herpesvirus 8 infection among adolescents in the REACH cohort. Arch Pediatr Adolesc Med **2006**; 160:937–42.
11. Butler LM, Were WA, Balinandi S, et al. Human herpesvirus 8 infection in children and adults in a population-based study in rural Uganda. J Infect Dis **2011**; 203:625–34.
12. Mbulaiteye SM, Biggar RJ, Bakaki PM, et al. Human herpesvirus 8 infection and transfusion history in children with sickle-cell disease in Uganda. J Natl Cancer Inst **2003**; 95:1330–5.
13. Dedicoat M, Newton R, Alkharsah KR, et al. Mother-to-child transmission of human herpesvirus-8 in South Africa. J Infect Dis **2004**; 190:1068–75.
14. de-The G, Bestetti G, van Beveren M, Gessain A. Prevalence of human herpesvirus 8 infection before the acquired immunodeficiency disease syndrome-related epidemic of Kaposi's sarcoma in East Africa. J Natl Cancer Inst **1999**; 91:1888–9.
15. Olsen SJ, Chang Y, Moore PS, et al. Increasing Kaposi's sarcoma-associated herpesvirus seroprevalence with age in a highly Kaposi's sarcoma endemic region, Zambia in 1985. AIDS **1998**; 12:1921–5.
16. Dollard SC, Butler LM, Jones AM, et al. Substantial regional differences in human herpesvirus 8 seroprevalence in sub-Saharan Africa: insights on the origin of the "Kaposi's sarcoma belt." Int J Cancer **2010**; 127:2395–401.
17. Cook-Mozaffari P, Newton R, Beral V, Burkitt DP. The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic. Br J Cancer **1998**; 78: 1521–8.
18. Sinfield RL, Molyneux EM, Banda K, et al. Spectrum and presentation of pediatric malignancies in the HIV era: experience from Blantyre, Malawi, 1998–2003. Pediatr Blood Cancer **2007**; 48:515–20.
19. Gantt S, Kakuru A, Wald A, et al. Clinical presentation and outcome of epidemic Kaposi sarcoma in Ugandan children. Pediatr Blood Cancer **2010**; 54:670–4.
20. Ziegler JL. Endemic Kaposi's sarcoma in Africa and local volcanic soils. Lancet **1993**; 342:1348–51.
21. Whitby D, Marshall VA, Bagni RK, et al. Reactivation of Kaposi's sarcoma-associated herpesvirus by natural products from Kaposi's sarcoma endemic regions. Int J Cancer **2007**; 120:321–8.
22. Geier SA, Baumann S, Goebel FD. Kaposi's sarcoma and volcanic soils. Lancet **1994**; 343:231–2.
23. Ruocco V, Ruocco E, Schwartz RA, Janniger CK. Kaposi sarcoma and quinine: a potentially overlooked triggering factor in millions of Africans. J Am Acad Dermatol **2011**; 64:434–6.
24. Coluzzi M, Manno D, Guzzinati S, et al. The bloodsucking arthropod bite as possible cofactor in the transmission of human herpesvirus-8 infection and in the expression of Kaposi's sarcoma disease. Parassitologia **2002**; 44:123–9.
25. Dedicoat M, Newton R. Review of the distribution of Kaposi's sarcoma-associated herpesvirus (KSHV) in Africa in relation to the incidence of Kaposi's sarcoma. Br J Cancer **2003**; 88:1–3.
26. Stefan DC, Stones DK, Wainwright L, Newton R. Kaposi sarcoma in South African children. Pediatr Blood Cancer **2011**; 56:392–6.

27. Chokunonga E, Levy LM, Bassett MT, et al. Cancer incidence in the African population of Harare, Zimbabwe: second results from the cancer registry 1993–1995. Int J Cancer **2000**; 85: 54–9.
28. Ziegler JL, Katongole-Mbidde E. Kaposi's sarcoma in childhood: an analysis of 100 cases from Uganda and relationship to HIV infection. Int J Cancer **1996**; 65:200–3.
29. Athale UH, Patil PS, Chintu C, Elem B. Influence of HIV epidemic on the incidence of Kaposi's sarcoma in Zambian children. J Acquir Immune Defic Syndr Hum Retrovirol **1995**; 8: 96–100.
30. Ganem D. KSHV and the pathogenesis of Kaposi sarcoma: listening to human biology and medicine. J Clin Invest **2010**; 120: 939–49.
31. Rezza G, Dorrucci M, Serraino D, et al. Incidence of Kaposi's sarcoma and HHV-8 seroprevalence among homosexual men with known dates of HIV seroconversion. Italian Seroconversion Study. AIDS **2000**; 14:1647–53.
32. Mosam A, Aboobaker J, Shaik F. Kaposi's sarcoma in sub-Saharan Africa: a current perspective. Current opinion in infectious diseases. **2010**; 23:119–23.
33. UNAIDS. Together We Will End AIDS. **2012**; pp 34. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/jc2296_unaids_togetherreport_2012_en.pdf. Accessed August 21, 2013.
34. Dittmer DP. Restricted Kaposi's sarcoma (KS) herpesvirus transcription in KS lesions from patients on successful antiretroviral therapy. MBio **2011**; 2:e00138-11.
35. Mani D, Neil N, Israel R, Aboulafia DM. A retrospective analysis of AIDS-associated Kaposi's sarcoma in patients with undetectable HIV viral loads and CD4 counts greater than 300 cells/mm$^3$. J Int Assoc Physicians AIDS Care (Chic) **2009**; 8:279–85.
36. Renne R, Lagunoff M, Zhong W, Ganem D. The size and conformation of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) DNA in infected cells and virions. J Virol **1996**; 70:8151–4.
37. Gradoville L, Gerlach J, Grogan E, et al. Kaposi's sarcoma-associated herpesvirus open reading frame 50/Rta protein activates the entire viral lytic cycle in the HH-B2 primary effusion lymphoma cell line. J Virol **2000**; 74: 6207–12.
38. Speck SH, Ganem D. Viral latency and its regulation: lessons from the gamma-herpesviruses. Cell Host Microbe **2010**; 8: 100–15.
39. Antman K, Chang Y. Kaposi's sarcoma. N Engl J Med **2000**; 342:1027–38.
40. Lu CC, Li Z, Chu CY, et al. MicroRNAs encoded by Kaposi's sarcoma-associated herpesvirus regulate viral life cycle. EMBO Rep **2010**; 11:784–90.
41. Dillon PJ, Gregory SM, Tamburro K, et al. Tousled-like kinases modulate reactivation of gammaherpesviruses from latency. Cell Host Microbe **2013**; 13:204–14.
42. Ye F, Zhou F, Bedolla RG, et al. Reactive oxygen species hydrogen peroxide mediates Kaposi's sarcoma-associated herpesvirus reactivation from latency. PLoS Pathog **2011**; 7:e1002054.
43. Blackbourn DJ, Fujimura S, Kutzkey T, Levy JA. Induction of human herpesvirus-8 gene expression by recombinant interferon gamma. AIDS **2000**; 14:98–9.
44. Chang J, Renne R, Dittmer D, Ganem D. Inflammatory cytokines and the reactivation of Kaposi's sarcoma-associated herpesvirus lytic replication. Virology **2000**; 266:17–25.
45. Harrington W Jr, Sieczkowski L, Sosa C, et al. Activation of HHV-8 by HIV-1 tat. Lancet **1997**; 349:774–5.
46. Ensoli B, Barillari G, Salahuddin SZ, et al. Tat protein of HIV-1 stimulates growth of cells derived from Kaposi's sarcoma lesions of AIDS patients. Nature **1990**; 345:84–6.
47. Martin JN, Ganem DE, Osmond DH, et al. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med **1998**; 338:948–54.
48. Pauk J, Huang ML, Brodie SJ, et al. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med **2000**; 343:1369–77.
49. Taylor MM, Chohan B, Lavreys L, et al. Shedding of human herpesvirus 8 in oral and genital secretions from HIV-1-seropositive and -seronegative Kenyan women. J Infect Dis **2004**; 190:484–8.
50. Plancoulaine S, Abel L, van Beveren M, et al. Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. Lancet **2000**; 356:1062–5.
51. Andreoni M, Sarmati L, Nicastri E, et al. Primary human herpesvirus 8 infection in immunocompetent children. JAMA **2002**; 287:1295–300.
52. Bourboulia D, Whitby D, Boshoff C, et al. Serologic evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus infection. JAMA **1998**; 280:31–2.
53. Malope BI, Pfeiffer RM, Mbisa G, et al. Transmission of Kaposi sarcoma-associated herpesvirus between mothers and children in a South African population. J Acquir Immune Defic Syndr **2007**; 44:351–5.
54. Mayama S, Cuevas LE, Sheldon J, et al. Prevalence and transmission of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in Ugandan children and adolescents. Int J Cancer **1998**; 77:817–20.
55. Edmunds WJ, Medley GF, Nokes DJ, et al. Epidemiological patterns of hepatitis B virus (HBV) in highly endemic areas. Epidemiol Infect **1996**; 117:313–25.
56. Mantina H, Kankasa C, Klaskala W, et al. Vertical transmission of Kaposi's sarcoma-associated herpesvirus. Int J Cancer **2001**; 94:749–52.
57. Ilboudo D, Simpore J, Sanou DS, et al. Mother-to-child HIV and HHV-8 transmission in neonates at Saint Camille Medical Centre in Burkina Faso. Pak J Biol Sci **2009**; 12:908–13.
58. Brayfield BP, Kankasa C, West JT, et al. Distribution of Kaposi sarcoma-associated herpesvirus/human herpesvirus 8 in maternal saliva and breast milk in Zambia: implications for transmission. J Infect Dis **2004**; 189:2260–70.
59. Gantt S, Carlsson J, Shetty AK, et al. Cytomegalovirus and Epstein-Barr virus in breast milk are associated with HIV-1 shedding but not with mastitis. AIDS **2008**; 22:1453–60.
60. Hladik W, Dollard SC, Mermin J, et al. Transmission of human herpesvirus 8 by blood transfusion. N Engl J Med **2006**; 355: 1331–8.
61. Hladik W, Pellett PE, Hancock J, et al. Association between transfusion with human herpesvirus 8 antibody-positive blood and subsequent mortality. J Infect Dis **2012**; 206:1497–503.
62. Minhas V, Brayfield BP, Crabtree KL, et al. Primary gammaherpesviral infection in Zambian children. BMC Infect Dis **2010**; 10:115.
63. Kasolo FC, Spinks J, Bima H, et al. Diverse genotypes of Kaposi's sarcoma associated herpesvirus (KSHV) identified in infant blood infections in African childhood-KS and HIV/AIDS endemic region. J Med Virol **2007**; 79:1555–61.
64. Luppi M, Barozzi P, Schulz TF, et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. N Engl J Med **2000**; 343:1378–85.
65. Olweny CL, Kaddumukasa A, Atine I, et al. Childhood Kaposi's sarcoma: clinical features and therapy. Br J Cancer **1976**; 33:555–60.
66. Cairncross LL, Davidson A, Millar AJ, Pillay K. Kaposi sarcoma in children with HIV: a clinical series from Red Cross Children's Hospital. J Pediatr Surg **2009**; 44:373–6.
67. Jacobson LP, Jenkins FJ, Springer G, et al. Interaction of human immunodeficiency virus type 1 and human herpesvirus type 8

infections on the incidence of Kaposi's sarcoma. J Infect Dis **2000**; 181:1940–9.
68. Renwick N, Halaby T, Weverling GJ, et al. Seroconversion for human herpesvirus 8 during HIV infection is highly predictive of Kaposi's sarcoma. AIDS **1998**; 12:2481–8.
69. Ramdial PK, Sing Y, Hadley GP, et al. Paediatric intussusception caused by acquired immunodeficiency syndrome-associated Kaposi sarcoma. Pediatr Surg Int **2010**; 26:783–7.
70. Gasparetto TD, Marchiori E, Lourenco S, et al. Pulmonary involvement in Kaposi sarcoma: correlation between imaging and pathology. Orphanet J Rare Dis **2009**; 4:18.
71. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS **2004**; 18:1615–27.
72. Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol **2005**; 23:5224–8.
73. Letang E, Almeida JM, Miro JM, et al. Predictors of immune reconstitution inflammatory syndrome-associated with Kaposi sarcoma in mozambique: a prospective study. J Acquir Immune Defic Syndr **2010**; 53:589–97.
74. Martin JL, Laker M, Kambugu A, et al. Kaposi's sarcoma-associated immune reconstitution inflammatory syndrome (KS-IRIS) in Africa: initial findings from a prospective evaluation. Infect Agent Cancer **2009**; 4(Suppl 2):O17.
75. Cox CM, El-Mallawany NK, Kabue M, et al. Clinical characteristics and outcomes of HIV-infected children diagnosed with Kaposi sarcoma in Malawi and Botswana. Pediatr Blood Cancer **2013**; 60:1274–80.
76. Vaz P, Macassa E, Jani I, et al. Treatment of Kaposi sarcoma in human immunodeficiency virus-1-infected Mozambican children with antiretroviral drugs and chemotherapy. Pediatr Infect Dis J **2011**; 30:891–3.
77. Le J, Gantt S, AST Infectious Diseases Community of Practice. Human herpesvirus 6, 7 and 8 in solid organ transplantation. Am J Transplant **2013**; 13(Suppl 4):128–37.
78. Celtik C, Unuvar A, Aydogan A, et al. Human herpes virus type 8-associated Kaposi sarcoma in a pediatric liver transplant recipient. Pediatr Transplant **2011**; 15:E100–4.
79. Marcelin AG, Roque-Afonso AM, Hurtova M, et al. Fatal disseminated Kaposi's sarcoma following human herpesvirus 8 primary infections in liver-transplant recipients. Liver Transpl **2004**; 10:295–300.
80. Yuksekkaya HA, Arikan C, Yazici A, et al. Successful treatment of a child having generalized Kaposi's sarcoma after living donor liver transplantation with conversion to sirolimus. Pediatr Transplant **2009**; 13:375–8.
81. Varela-Fascinetto G, Hernandez-Plata JA, Nieto-Zermeno J, et al. Pediatric liver transplant program at Hospital Infantil de Mexico Federico Gomez. Rev Invest Clin **2011**; 63(Suppl 1): 57–61.
82. Sala I, Faraci M, Magnano GM, et al. HHV-8-related visceral Kaposi's sarcoma following allogeneic HSCT: report of a pediatric case and literature review. Pediatr Transplant **2011**; 15: E8–11.
83. Porta F, Bongiorno M, Locatelli F, et al. Kaposi's sarcoma in a child after autologous bone marrow transplantation for non-Hodgkin's lymphoma. Cancer **1991**; 68:1361–4.
84. Tamariz-Martel R, Maldonado MS, Carrillo R, et al. Kaposi's sarcoma after allogeneic bone marrow transplantation in a child. Haematologica **2000**; 85:884–5.
85. Abbas AA, Jastaniah WA. Extensive gingival and respiratory tract Kaposi sarcoma in a child after allogenic hematopoietic stem cell transplantation. J Pediatr Hematol Oncol **2012**; 34: e53–5.
86. Martinez S, McAdams HP, Youens KE. Kaposi sarcoma after bilateral lung transplantation. J Thorac Imaging **2008**; 23:50–3.
87. Riva G, Luppi M, Barozzi P, et al. How I treat HHV8/KSHV-related diseases in posttransplant patients. Blood **2012**; 120:4150–9.
88. Grossman WJ, Radhi M, Schauer D, et al. Development of hemophagocytic lymphohistiocytosis in triplets infected with HHV-8. Blood **2005**; 106:1203–6.
89. Fardet L, Blum L, Kerob D, et al. Human herpesvirus 8-associated hemophagocytic lymphohistiocytosis in human immunodeficiency virus-infected patients. Clin Infect Dis **2003**; 37:285–91.
90. Pasic S, Cupic M, Lazarevic I. HHV-8-related hemophagocytic lymphohistiocytosis in a boy with XLP phenotype. J Pediatr Hematol Oncol **2012**; 34:467–71.
91. Sanchez-Velasco P, Ocejo-Vinyals JG, Flores R, et al. Simultaneous multiorgan presence of human herpesvirus 8 and restricted lymphotropism of Epstein-Barr virus DNA sequences in a human immunodeficiency virus-negative immunodeficient infant. J Infect Dis **2001**; 183:338–42.
92. Simpson GR, Schulz TF, Whitby D, et al. Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet **1996**; 348:1133–8.
93. Gao SJ, Kingsley L, Li M, et al. KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nat Med **1996**; 2:925–8.
94. Engels EA, Sinclair MD, Biggar RJ, et al. Latent class analysis of human herpesvirus 8 assay performance and infection prevalence in sub-Saharan Africa and Malta. Int J Cancer **2000**; 88: 1003–8.
95. Spira TJ, Lam L, Dollard SC, et al. Comparison of serologic assays and PCR for diagnosis of human herpesvirus 8 infection. J Clin Microbiol **2000**; 38:2174–80.
96. Engels EA, Biggar RJ, Marshall VA, et al. Detection and quantification of Kaposi's sarcoma-associated herpesvirus to predict AIDS-associated Kaposi's sarcoma. AIDS **2003**; 17: 1847–51.
97. Dittmer DP. Transcription profile of Kaposi's sarcoma-associated herpesvirus in primary Kaposi's sarcoma lesions as determined by real-time PCR arrays. Cancer Res **2003**; 63: 2010–5.
98. Arkin LM, Cox CM, Kovarik CL. Kaposi's sarcoma in the pediatric population: the critical need for a tissue diagnosis. Pediatr Infect Dis J **2009**; 28:426–8.
99. Dupuy S, Lambert M, Zucman D, et al. Human herpesvirus 8 (HHV8) sequentially shapes the NK cell repertoire during the course of asymptomatic infection and Kaposi sarcoma. PLoS Pathog **2012**; 8:e1002486.
100. Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol **1989**; 7: 1201–7.
101. Krown SE, Testa MA, Huang J. AIDS-related Kaposi's sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. AIDS Clinical Trials Group Oncology Committee. J Clin Oncol **1997**; 15:3085–92.
102. Nasti G, Talamini R, Antinori A, et al. AIDS-related Kaposi's sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the Haart Era–the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive From Antiretrovirals. J Clin Oncol **2003**; 21:2876–82.
103. Dedicoat M, Vaithilingum M, Newton R. Treatment of Kaposi's sarcoma in HIV-1 infected individuals with emphasis on resource poor settings. Cochrane Database Syst Rev **2003**; CD003256.

104. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep **2009**; 58 (RR-11);1–166.
105. Bower M, Fox P, Fife K, et al. Highly active anti-retroviral therapy (HAART) prolongs time to treatment failure in Kaposi's sarcoma. AIDS **1999**; 13:2105–11.
106. Martellotta F, Berretta M, Vaccher E, et al. AIDS-related Kaposi's sarcoma: state of the art and therapeutic strategies. Curr HIV Res **2009**; 7:634–8.
107. Chow WA, Jiang C, Guan M. Anti-HIV drugs for cancer therapeutics: back to the future? Lancet Oncol **2009**; 10:61–71.
108. Gantt S, Casper C. Human herpesvirus 8-associated neoplasms: the roles of viral replication and antiviral treatment. Curr Opin Infect Dis **2011**; 24:295–301.
109. Molyneux E, Davidson A, Orem J, et al. The management of children with Kaposi sarcoma in resource limited settings. Pediatr Blood Cancer **2013**; 60:538–42.
110. Krown SE. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. J Clin Oncol **2004**; 22:399–402.
111. Mosam A, Shaik F, Uldrick TS, et al. A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy-naive patients with HIV-associated Kaposi sarcoma in South Africa. J Acquir Immune Defic Syndr **2012**; 60:150–7.
112. Martin DF, Kuppermann BD, Wolitz RA, et al. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. New Engl J Med **1999**; 340:1063–70.
113. Casper C, Krantz EM, Corey L, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. J Infect Dis **2008**; 198:23–30.
114. Grzegorzewska AE, Frankiewicz D, Breborowicz D, et al. Disseminated cutaneous Kaposi sarcoma in a patient receiving triptolide/tripdiolide for rheumatoid arthritis. Med Sci Monit **2012**; 18:CS67–71.
115. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nat Rev Cancer **2010**; 10:707–19.
116. Lagos D, Vart RJ, Gratrix F, et al. Toll-like receptor 4 mediates innate immunity to Kaposi sarcoma herpesvirus. Cell Host Microbe **2008**; 4:470–83.