Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

Visit the AIDS*info* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at https://aidsinfo.nih.gov/e-news.

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

Human Herpesvirus 8 Disease (Last updated December 15, 2016; last reviewed December 15, 2016)

Panel's Recommendations
I. **Is there an indication for serologic testing for human herpesvirus 8 (HHV-8) in asymptomatic HIV-infected children (compared with not testing) to guide clinical management?** Antibody (or DNA testing) for HHV-8 is insufficiently sensitive/specific to predict risk of Kaposi sarcoma. Therefore, routine testing to identify HHV-8-seropositive, HIV-infected patients is not recommended (**strong, very low**).
II. Among HIV-infected children, does initiation of antiretroviral therapy (ART) (as compared with non-initiation) reduce the risk of Kaposi sarcoma? Effective suppression of HIV replication with ART is recommended to reduce the risk of HHV-8-associated Kaposi sarcoma (**strong, low**).
III. For HIV-infected patients initiating ART, are any specific ART regimens associated with lower rates of Kaposi sarcoma? Data are insufficient and conflicting upon which to base a recommendation for a particular ART regimen for prevention of Kaposi sarcoma (**weak, low**).
IV. Among HIV-infected children with active Kaposi sarcoma, is treatment with ART (as compared with no ART) associated with higher rates of remission and/or decreased mortality? Treatment with ART is associated with increased survival among HIV-infected children with active Kaposi sarcoma. Effective suppression of HIV replication with ART is recommended for all patients with evidence of active Kaposi sarcoma and other HHV-8-associated malignant lymphoproliferative disorders (**strong, very low**).
V. Among HIV-infected children with active Kaposi sarcoma, is treatment with chemotherapy in addition to ART (as compared with ART alone) associated with higher rates of remission and/or decreased mortality? Systemic chemotherapy, in addition to ART, is associated with higher rates of remission and decreased mortality and is recommended for disseminated or visceral Kaposi sarcoma (stage T1 disease) and for primary effusion lymphoma (**strong, low**). For localized Kaposi sarcoma (stage T0 disease), the benefit of systemic chemotherapy (in addition to ART) is unclear.
VI. Among HIV-infected children treated with ART who develop immune reconstitution inflammatory syndrome (IRIS), is chemotherapy in addition to continuation of ART (compared with no chemotherapy) associated with higher rates of remission and/or decreased mortality? For patients with Kaposi-sarcoma-associated IRIS, chemotherapy along with continuation of ART is recommended (**strong, low**).
VII. Among HIV-infected children who achieve remission from Kaposi sarcoma, what therapies are recommended to lower the risk of recurrence? Effective suppression of HIV replication with ART in HIV-infected patients with Kaposi sarcoma may prevent Kaposi sarcoma progression or occurrence of new lesions and may decrease risk of recurrence after remission. Life-long ART is recommended for all individuals with evidence of active or treated Kaposi sarcoma or other HHV-8-associated malignant lymphoproliferative disorders (**strong, low**).
Rating System *Strength of Recommendation:* Strong; Weak *Quality of Evidence:* High; Moderate; Low; or Very Low

Introduction/Overview

Epidemiology

Human herpesvirus 8 (HHV-8), also called Kaposi sarcoma (KS)-associated herpesvirus (KSHV), is a gamma human herpesvirus most closely related to Epstein-Barr virus. HHV-8 has been causally linked to all forms of KS (i.e., HIV-related, classic endemic, and iatrogenic) and with two rare neoplastic conditions usually associated with HIV infection: body cavity-based lymphoma, also known as primary effusion lymphoma (a B-cell lymphoma that typically arises in body cavities such as the pleural space), and multicentric Castleman disease (non-cancerous tumors that may develop in lymph nodes in a single site or in multiple sites throughout the body). The exact mechanism by which HHV-8 infection leads to neoplastic disease has not been fully elucidated, but seroconversion to HHV-8 antibody positivity virtually always

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

precedes development of the tumors.[1]

The prevalence of antibodies to HHV-8 varies widely with age, geography, and certain risk factors. In the United States and Europe, 1% to 3% of the general adult population is seropositive, with higher rates (8%) among men who have sex with men (MSM).[2] In a U.S. cohort of HIV-infected and at-risk (but HIV-negative) adolescents with a median age of 19 years, 11.2% were HHV-8 seropositive.[3] The highest rates were in adolescent HIV-infected MSM (23%). Seropositivity was associated with HIV infection, MSM, a history of syphilis, and injection-drug use.[3,4] The general adult seropositivity rate in Mediterranean countries ranges from 10% to 25%. In areas where HHV-8 is endemic, such as eastern and central sub-Saharan Africa, HHV-8 seropositivity rates as high as 80% have been reported in adults.[5-9]

HHV-8 is transmitted through oral and, possibly, genital secretions. Immunocompetent HHV-8-infected adults frequently shed HHV-8 in their oropharyngeal secretions.[10] In areas where HHV-8 infection is endemic, the seroprevalence increases quickly during the first 5 years of life (especially when other family members are HHV-8-positive), then plateaus until adolescence and young adult years.[11,12] The seroprevalence among infants and children increases with the number of HHV-8-positive parents and siblings in the home, indicating non-sexual transmission for prepubertal children, with a limited role for perinatal transmission.[11-18] HHV-8 can also be transmitted through exposure to infected blood, including through intravenous (IV) drug use and blood product transfusions.[19]

For HIV-infected individuals, coinfection with HHV-8 places them at increased risk of KS. Most cases of KS occur in adults (compared with children). Before the advent of antiretroviral therapy (ART), the overall incidence of KS in HIV-infected adults was as high as 20%. However, in the United States and England, KS represented less than 1% of pediatric AIDS-defining illnesses, likely due in part to low HHV-8 seroprevalence in children in these regions. Although KS occurs primarily in adults, the incidence in children has increased dramatically as a result of the HIV pandemic, particularly in sub-Saharan Africa.[20-22] Iatrogenic KS has emerged as well, predominantly among adults in developed settings, with increasing use of immunosuppressive therapies and organ transplantation.[23] Pediatric cases of iatrogenic KS after liver or bone marrow transplantation have also been described.[24-27]

The risk of KS among HIV-infected individuals is highest among those with severe immunodeficiency. KS, primary effusion lymphoma, and multicentric Castleman disease can occur at any CD4 T lymphocyte (CD4) cell count, but they are described most often in HIV-infected patients with more advanced immunosuppression (CD4 cell count <200 cells/mm^3 in adults). It should be noted, however, that 5% to 10% of newly diagnosed KS in adults occurs in those with CD4 cell count >300/mm^3 and/or low or undetectable plasma HIV RNA levels.[28,29]

The incidence of KS appeared to decline in the United States even before the widespread use of ART. The reason is unclear but may have been related to the use of other antiviral agents, such as those used to treat cytomegalovirus (CMV) (i.e., foscarnet, ganciclovir, and cidofovir), which may inhibit HHV-8.[30-36] The incidence of KS in adults has continued to decrease with the advent of earlier and more aggressive ART.

Clinical Manifestations

Primary infection with HHV-8 in young, immunocompetent children may be asymptomatic or may present as a self-limited mononucleosis-like illness consisting of fever, mild upper respiratory symptoms, and a maculopapular rash. A similar presentation has been described in immunocompetent adults.[37,38] A more severe illness has been described in immunocompromised patients, who may present with disseminated infection with fever, lymphadenopathy, splenomegaly, and pancytopenia.[39,40] Reactivation of HHV-8 has been associated with hemophagocytic lymphohistiocytosis in HIV-infected adults.[41]

KS presentation varies widely, with cutaneous, oral, lymphatic, or visceral involvement, or some combination of the three.[42,43] Pediatric presentations differ from those of adults and are best described in retrospective cohort studies from sub-Saharan Africa.[21,43-45] Cutaneous forms involve characteristic non-

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

tender, purplish, indurated skin lesions, which may be seen in 47% to 83% of affected children. Children also commonly present with lymphatic involvement (30% to 64%), a particularly aggressive form of the disease, and as many as 10% to 18% of these children may not have skin lesions. Intraoral lesions may be seen in 21% to 41%, occasionally (4%) without skin lesions. Visceral dissemination occurs in 12% to 38% of children. Median age at presentation in these studies ranges from 6 years to 10 years, and KS has been diagnosed in children as young as 10 months to 2 years. Median CD4 percentage at presentation in these studies ranges from 7.4% to 16%.

Multicentric Castleman disease presents with generalized adenopathy and fever and may progress to multi-organ failure. Primary effusion lymphoma presents with symptoms related to fluid accumulation in the pleural or pericardial space or with abdominal distention.

Diagnosis

Laboratory diagnosis of HHV-8 infection is most commonly based on serologic assays, such as immunofluorescence, enzyme-linked immunosorbent assay, and Western blot. However, there is no gold standard for diagnosing HHV-8 infection. Serologic tests range in sensitivity from 80% to ≥90% and interassay agreement is poor.[46] Combination assays containing both lytic and late-phase antigens may improve detection rates. Nucleic acid-based tests, such as in situ DNA hybridization and polymerase chain reaction (PCR), are important for tissue diagnosis. Although these tests have high levels of sensitivity, their specificity and reproducibility are highly variable. Only 40% to 60% of patients with proven KS will have HHV-8 DNA in their blood or saliva detectable by PCR, and in them, positivity will vary over time.

Diagnosis of KS requires biopsy and histologic examination of affected tissues.

Prevention Recommendations

Preventing Exposure

Routine testing of children and adults for HHV-8 is not recommended; therefore, the serostatus of HIV-infected patients usually is unknown. Although the efficacy of condoms in preventing HHV-8 exposure has not been established, HIV-infected patients should use male latex condoms correctly and consistently during sexual intercourse to reduce exposure to sexually transmitted pathogens.

Preventing First Episode of Disease

The use of ART with suppression of HIV replication has markedly decreased the incidence of KS in HIV-infected adults. Several antiviral agents (i.e., ganciclovir, foscarnet, and cidofovir) inhibit HHV-8 replication *in vitro*, and data suggest that their use can prevent KS in patients who are HIV/HHV-8 coinfected.[47] However, antiviral use for prevention of KS is not currently recommended.

Treatment Recommendations

Treating Disease

Specific treatment regimens are not included in this report because the HIV-related clinical entities associated with HHV-8, such as KS and Castleman disease, are oncologic and traditionally have been treated with cytotoxic chemotherapy. However, in HIV-infected patients with KS, effective suppression of HIV replication with ART may result in improvement in KS lesions, prevent KS progression, or prevent occurrence of new KS lesions. Therefore, ART is recommended for all HIV-infected patients with evidence of active KS and other HHV-8-associated malignant lymphoproliferative disorders.

In HIV-infected adults with KS, HHV-8 cellular viremia and higher viral load have been associated with disease progression.[48] The vast majority of infected cells are not undergoing lytic replication, and anti-herpesvirus medications have had little or no effect on established KS or HHV-8 cellular viremia. Studies are under way of methods that induce lytic replication or attack the episomal (latent) HHV-8 genome.[49,50]

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

In contrast to KS, in Castleman disease, many of the cells support lytic replication of HHV-8, and treatment with anti-herpesvirus drugs has led to substantial clinical improvement in some studies.[50] IV ganciclovir or oral valganciclovir may be considered for treating multicentric Castleman disease[51] and may be a useful adjunct for treating primary effusion lymphoma.[52,53] These diagnoses are exceedingly rare in children; in such cases, adult guidelines should be consulted.

Monitoring and Adverse Events (Including IRIS)

KS-associated immune reconstitution inflammatory syndrome (KS-IRIS) generally describes the appearance of or paradoxical clinical worsening of KS after initiation of a potent ART regimen. KS-IRIS is not predicted by low CD4 cell count.[54] KS-IRIS is associated with higher mortality than KS not associated with IRIS. In African cohorts, where mortality from KS-IRIS is high, chemotherapy in addition to ART was associated with increased survival.[55]

For patients with disease manifestations of HHV-8 infection who are treated with ganciclovir or valganciclovir, refer to the chapter on CMV infections (Monitoring and Adverse Events) for information on treatment-associated adverse events.

Preventing Recurrence

Effective suppression of HIV replication with ART in HIV-infected patients with KS may result in improvement in KS lesions, prevent KS progression, or prevent occurrence of new KS lesions and is recommended for all individuals with evidence of active KS and other HHV-8-associated malignant lymphoproliferative disorders.

Primary Prevention

I. Is there an indication for serologic testing for HHV-8 in asymptomatic HIV-infected children (compared with not testing) to guide clinical management?

Routine testing to identify HHV-8-seropositive, HIV-infected patients is not recommended (**strong, very low**).

Although KS is one of the most common cancers in HIV-infected individuals, a minority of coinfected individuals will develop KS. Seroprevalence of HHV-8 varies by country, but in some areas reaches ≥50% by adulthood. Sensitivity and specificity of antibody testing vary, and HHV-8 DNA shedding in saliva and presence in plasma are not consistent. Studies are conflicting on utility of quantitative DNA PCR for prediction of risk of KS in HHV-8-seropositive, HIV-infected adults. Based on lack of accurate prediction of risk of KS by antibody and HHV-8 DNA assays, routine testing is not indicated. For someone known to be HHV-8-seropositive, that factor should be considered in discussions about ART initiation.

II. Among HIV-infected children, does initiation of ART (as compared with non-initiation) reduce the risk of KS?

Effective suppression of HIV replication with ART is recommended to reduce the risk of HHV-8-associated KS (**strong, low**).

Multiple observational studies in adults have shown that the incidence of KS is drastically reduced in adults on ART.[56,57] In one retrospective pediatric study, 0 of 1,000 children on ART developed KS, in contrast with 32 children out of 3,000 who presented with or developed KS prior to starting ART.[45]

III. For HIV-infected patients initiating ART, are any specific ART regimens associated with lower rates of KS?

Data are insufficient and conflicting on which to base a recommendation for a particular ART regimen for prevention of KS (**weak, low**).

Evidence has been conflicting as to whether non-nucleoside reverse transcriptase inhibitor (NNRTI)- or

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

protease inhibitor (PI)-based ART has an advantage in the prevention of KS. Laboratory evidence of PI antitumor activity exists, most notably for nelfinavir, but also for ritonavir and ritonavir-boosted lopinavir. In addition, there is preliminary evidence that PI-based therapy reduces HHV-8 DNA oropharyngeal shedding.[58] One recent, large observational study of adults noted an advantage for PI-based therapy over NNRTI-based regimens in the prevention of KS, but other studies have found no difference between regimens.[56,57] There are no corresponding data from pediatric studies. It should be noted that 5% to 10% of new cases of KS in adults occur in those on therapy, with undetectable viral loads and/or CD4 cell counts >300 cells/mm^3.[28,29]

Treatment

IV. Among HIV-infected children with active KS, is treatment with ART (as compared with no ART) associated with higher rates of remission and/or decreased mortality?

Effective suppression of HIV replication with ART is recommended for all patients with evidence of active KS and/or other HHV-8-associated malignant lymphoproliferative disorders (**strong, very low**).

Treatment with ART is first-line therapy against KS and other HHV-8-associated malignant proliferative disorders, and is associated with increased survival among HIV-infected children with active KS.[21,44,58]

V. Among HIV-infected children with active KS, is treatment with chemotherapy in addition to ART (as compared with ART alone) associated with higher rates of remission and/or decreased mortality?

Systemic chemotherapy, in addition to ART, is associated with higher rates of remission and decreased mortality and is recommended for disseminated or visceral KS (stage T1 disease) and for primary effusion lymphoma (**strong, low**). For localized KS (stage T0 disease), the benefit of systemic chemotherapy (in addition to ART) is unclear.

There is a paucity of information to guide the clinical management of HIV-infected children with KS. The available studies were retrospective, had relatively small sample sizes, and were performed in sub-Saharan Africa.[44,45,58] Data from these studies were not adjusted for KS stage or for comorbidities. Additionally, AIDS Clinical Trials Group staging classification has not been validated in children. For focal or early stage KS, HIV-infected adults have been effectively treated with ART alone.[59] Local intralesional chemotherapy or radiation therapy may be considered for focal disease. The available evidence in children suggests that systemic chemotherapy in addition to ART is associated with increased likelihood of remission and decreased mortality. It is unclear, however, if localized disease (stage T0) can be treated effectively without systemic chemotherapy. Data are insufficient on which to base a recommendation for a particular chemotherapy regimen, and various regimens have been used in different settings. Patient clinical presentation and available therapies in the practice setting should be considered, in consultation with an oncologist.

VI. Among HIV-infected children treated with ART who develop IRIS, is chemotherapy in addition to continuation of ART (compared with no chemotherapy) associated with higher rates of remission and/or decreased mortality?

For patients with KS-associated IRIS, chemotherapy along with continuation of ART is recommended (**strong, low**).

Studies of HIV-infected adults with KS-associated IRIS (primarily from African cohorts) indicate that chemotherapy in addition to ART, as opposed to ART alone, is associated with reduced mortality.[55,60]

Secondary Prevention

VII. Among HIV-infected children who achieve remission from KS, what therapies are recommended to lower the risk of recurrence?

Effective suppression of HIV replication with ART in HIV-infected patients with KS may prevent KS progression or occurrence of new lesions and is recommended for all individuals with evidence of active or treated KS and/or other HHV-8-associated malignant lymphoproliferative disorders (**strong, low**).

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

The risk of KS recurrence has decreased in the ART era. In 1 study of adults treated with pegylated liposomal doxorubicin and ART (which continued after chemotherapy), the relapse rate was 13.5% per year, and was highest in the first year.[61] In 1 large Italian study, a multivariate analysis demonstrated a strong association between use of ART and increased 10-year survival rates after KS.[62]

References

1. Gao SJ, Kingsley L, Hoover DR, et al. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. *N Engl J Med*. 1996;335(4):233-241. Available at http://www.ncbi.nlm.nih.gov/pubmed/8657239.

2. Engels EA, Atkinson JO, Graubard BI, et al. Risk factors for human herpesvirus 8 infection among adults in the United States and evidence for sexual transmission. *J Infect Dis*. 2007;196(2):199-207. Available at http://www.ncbi.nlm.nih.gov/pubmed/17570106.

3. Casper C, Meier AS, Wald A, Morrow RA, Corey L, Moscicki AB. Human herpesvirus 8 infection among adolescents in the REACH cohort. *Arch Pediatr Adolesc Med*. 2006;160(9):937-942. Available at http://www.ncbi.nlm.nih.gov/pubmed/16953017.

4. Cannon MJ, Dollard SC, Smith DK, et al. Blood-borne and sexual transmission of human herpesvirus 8 in women with or at risk for human immunodeficiency virus infection. *N Engl J Med*. 2001;344(9):637-643. Available at http://www.ncbi.nlm.nih.gov/pubmed/11228278.

5. Whitby D, Smith NA, Matthews S, et al. Human herpesvirus 8: seroepidemiology among women and detection in the genital tract of seropositive women. *J Infect Dis*. 1999;179(1):234-236. Available at http://www.ncbi.nlm.nih.gov/pubmed/9841845.

6. Goedert JJ, Kedes DH, Ganem D. Antibodies to human herpesvirus 8 in women and infants born in Haiti and the USA. *Lancet*. 1997;349(9062):1368. Available at http://www.ncbi.nlm.nih.gov/pubmed/9149705.

7. Huang LM, Huang SY, Chen MY, et al. Geographical differences in human herpesvirus 8 seroepidemiology: a survey of 1,201 individuals in Asia. *J Med Virol*. 2000;60(3):290-293. Available at http://www.ncbi.nlm.nih.gov/pubmed/10630961.

8. Serraino D, Locatelli M, Songini M, et al. Human herpes virus-8 infection among pregnant women and their children: results from the Sardinia-IDDM Study 2. *Int J Cancer*. 2001;91(5):740-741. Available at http://www.ncbi.nlm.nih.gov/pubmed/11267990.

9. Martin JN. The Epidemiology Of KSHV andits Association with Malignant Disease. In: Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Cambridge: Cambridge University Press; 2007. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21348075.

10. Casper C, Krantz E, Selke S, et al. Frequent and asymptomatic oropharyngeal shedding of human herpesvirus 8 among immunocompetent men. *J Infect Dis*. 2007;195(1):30-36. Available at http://www.ncbi.nlm.nih.gov/pubmed/17152006.

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(5):625-634. Available at http://www.ncbi.nlm.nih.gov/pubmed/21273188.

12. Mbulaiteye SM, Pfeiffer RM, Whitby D, Brubaker GR, Shao J, Biggar RJ. Human herpesvirus 8 infection within families in rural Tanzania. *J Infect Dis*. 2003;187(11):1780-1785. Available at http://www.ncbi.nlm.nih.gov/pubmed/12751036.

13. He J, Bhat G, Kankasa C, et al. Seroprevalence of human herpesvirus 8 among Zambian women of childbearing age without Kaposi's sarcoma (KS) and mother-child pairs with KS. *J Infect Dis*. 1998;178(6):1787-1790. Available at http://www.ncbi.nlm.nih.gov/pubmed/9815235.

14. Gessain A, Mauclere P, van Beveren M, et al. Human herpesvirus 8 primary infection occurs during childhood in Cameroon, Central Africa. *Int J Cancer*. 1999;81(2):189-192. Available at http://www.ncbi.nlm.nih.gov/

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

pubmed/10188717.

15. Sitas F, Newton R, Boshoff C. Increasing probability of mother-to-child transmission of HHV-8 with increasing maternal antibody titer for HHV-8. *N Engl J Med*. 1999;340(24):1923. Available at http://www.ncbi.nlm.nih.gov/pubmed/10375309.

16. Calabro ML, Gasperini P, Barbierato M, et al. A search for human herpesvirus 8 (HHV-8) in HIV-1 infected mothers and their infants does not suggest vertical transmission of HHV-8. *Int J Cancer*. 2000;85(2):296-297. Available at http://www.ncbi.nlm.nih.gov/pubmed/10629092.

17. 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(9235):1062-1065. Available at http://www.ncbi.nlm.nih.gov/pubmed/11009141.

18. 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(3):351-355. Available at http://www.ncbi.nlm.nih.gov/pubmed/17195763.

19. Hladik W, Dollard SC, Mermin J, et al. Transmission of human herpesvirus 8 by blood transfusion. *N Engl J Med*. 2006;355(13):1331-1338. Available at http://www.ncbi.nlm.nih.gov/pubmed/17005950.

20. 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(2):200-203. Available at http://www.ncbi.nlm.nih.gov/pubmed/8567117.

21. Stefan DC, Stones DK, Wainwright L, Newton R. Kaposi sarcoma in South African children. *Pediatr Blood Cancer*. 2011;56(3):392-396. Available at http://www.ncbi.nlm.nih.gov/pubmed/21225916.

22. Tukei VJ, Kekitiinwa A, Beasley RP. Prevalence and outcome of HIV-associated malignancies among children. *AIDS*. 2011;25(14):1789-1793. Available at http://www.ncbi.nlm.nih.gov/pubmed/21673560.

23. Le J, Gantt S, Practice ASTIDCo. Human herpesvirus 6, 7 and 8 in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:128-137. Available at http://www.ncbi.nlm.nih.gov/pubmed/23465006.

24. 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(6):1361-1364. Available at http://www.ncbi.nlm.nih.gov/pubmed/1873788.

25. Yuksekkaya HA, Arikan C, Yazici A, Baran M, Aydogdu S, Kilic M. Successful treatment of a child having generalized Kaposi's sarcoma after living donor liver transplantation with conversion to sirolimus. *Pediatr Transplant*. 2009;13(3):375-378. Available at http://www.ncbi.nlm.nih.gov/pubmed/18452496.

26. 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(5):E100-104. Available at http://www.ncbi.nlm.nih.gov/pubmed/20214749.

27. 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(2):e53-55. Available at http://www.ncbi.nlm.nih.gov/pubmed/22217492.

28. 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(5):279-285. Available at http://www.ncbi.nlm.nih.gov/pubmed/19721098.

29. Franceschi S, Maso LD, Rickenbach M, et al. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *Br J Cancer*. 2008;99(5):800-804. Available at http://www.ncbi.nlm.nih.gov/pubmed/18665172.

30. Glesby MJ, Hoover DR, Weng S, et al. Use of antiherpes drugs and the risk of Kaposi's sarcoma: data from the Multicenter AIDS Cohort Study. *J Infect Dis*. 1996;173(6):1477-1480. Available at http://www.ncbi.nlm.nih.gov/

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

pubmed/8648224.

31. Mocroft A, Youle M, Gazzard B, Morcinek J, Halai R, Phillips AN. Anti-herpesvirus treatment and risk of Kaposi's sarcoma in HIV infection. Royal Free/Chelsea and Westminster Hospitals Collaborative Group. *AIDS*. 1996;10(10):1101-1105. Available at http://www.ncbi.nlm.nih.gov/pubmed/8874626.

32. Cannon JS, Hamzeh F, Moore S, Nicholas J, Ambinder RF. Human herpesvirus 8-encoded thymidine kinase and phosphotransferase homologues confer sensitivity to ganciclovir. *J Virol*. 1999;73(6):4786-4793. Available at http://www.ncbi.nlm.nih.gov/pubmed/10233939.

33. Neyts J, De Clercq E. Antiviral drug susceptibility of human herpesvirus 8. *Antimicrob Agents Chemother*. 1997;41(12):2754-2756. Available at http://www.ncbi.nlm.nih.gov/pubmed/9420052.

34. Kedes DH, Ganem D. Sensitivity of Kaposi's sarcoma-associated herpesvirus replication to antiviral drugs. Implications for potential therapy. *J Clin Invest*. 1997;99(9):2082-2086. Available at http://www.ncbi.nlm.nih.gov/pubmed/9151779.

35. Robles R, Lugo D, Gee L, Jacobson MA. Effect of antiviral drugs used to treat cytomegalovirus end-organ disease on subsequent course of previously diagnosed Kaposi's sarcoma in patients with AIDS. *J Acquir Immune Defic Syndr* Hum Retrovirol. 1999;20(1):34-38. Available at http://www.ncbi.nlm.nih.gov/pubmed/9928727.

36. Cannon MJ, Laney AS, Pellett PE. Human herpesvirus 8: current issues. *Clin Infect Dis*. 2003;37(1):82-87. Available at http://www.ncbi.nlm.nih.gov/pubmed/12830412.

37. Chen RL, Lin JC, Wang PJ, Lee CP, Hsu YH. Human herpesvirus 8-related childhood mononucleosis: a series of three cases. *Pediatr Infect Dis J*. 2004;23(7):671-674. Available at http://www.ncbi.nlm.nih.gov/pubmed/15247609.

38. Andreoni M, Sarmati L, Nicastri E, et al. Primary human herpesvirus 8 infection in immunocompetent children. *JAMA*. 2002;287(10):1295-1300. Available at http://www.ncbi.nlm.nih.gov/pubmed/11886321.

39. 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(19):1378-1385. Available at http://www.ncbi.nlm.nih.gov/pubmed/11070102.

40. Luppi M, Barozzi P, Rasini V, et al. Severe pancytopenia and hemophagocytosis after HHV-8 primary infection in a renal transplant patient successfully treated with foscarnet. *Transplantation*. 2002;74(1):131-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/12134112.

41. 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(2):285-291. Available at http://www.ncbi.nlm.nih.gov/pubmed/12856221.

42. Dow DE, Cunningham CK, Buchanan AM. A Review of Human Herpesvirus 8, the Kaposi's Sarcoma-Associated Herpesvirus, in the Pediatric Population. *J Pediatric Infect Dis Soc*. 2014;3(1):66-76. Available at http://www.ncbi.nlm.nih.gov/pubmed/24567845.

43. Gantt S, Kakuru A, Wald A, et al. Clinical presentation and outcome of epidemic Kaposi sarcoma in Ugandan children. *Pediatr Blood Cancer*. 2010;54(5):670-674. Available at http://www.ncbi.nlm.nih.gov/pubmed/20205254.

44. 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(8):1274-1280. Available at http://www.ncbi.nlm.nih.gov/pubmed/23487320.

45. 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(10):891-893. Available at http://www.ncbi.nlm.nih.gov/pubmed/21730886.

46. Bhaduri-McIntosh S. Human herpesvirus-8: clinical features of an emerging viral pathogen. *Pediatr Infect Dis J*. 2005;24(1):81-82. Available at http://www.ncbi.nlm.nih.gov/pubmed/15665715.

47. Gantt S, Casper C. Human herpesvirus 8-associated neoplasms: the roles of viral replication and antiviral treatment.

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

Curr Opin Infect Dis. 2011;24(4):295-301. Available at http://www.ncbi.nlm.nih.gov/pubmed/21666458.

48. Laney AS, Cannon MJ, Jaffe HW, et al. Human herpesvirus 8 presence and viral load are associated with the progression of AIDS-associated Kaposi's sarcoma. *AIDS*. 2007;21(12):1541-1545. Available at http://www.ncbi.nlm.nih.gov/pubmed/17630548.

49. Anderson LA, Goedert JJ. Tumor markers and treatments for Kaposi sarcoma. *AIDS*. 2007;21(12):1637-1639. Available at http://www.ncbi.nlm.nih.gov/pubmed/17630560.

50. Klass CM, Offermann MK. Targeting human herpesvirus-8 for treatment of Kaposi's sarcoma and primary effusion lymphoma. *Curr Opin Oncol*. 2005;17(5):447-455. Available at http://www.ncbi.nlm.nih.gov/pubmed/16093794.

51. Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. *Blood*. 2004;103(5):1632-1634. Available at http://www.ncbi.nlm.nih.gov/pubmed/14615380.

52. Aboulafia DM. Interleukin-2, ganciclovir, and high-dose zidovudine for the treatment of AIDS-associated primary central nervous system lymphoma. *Clin Infect Dis*. 2002;34(12):1660-1662. Available at http://www.ncbi.nlm.nih.gov/pubmed/12032910.

53. Crum-Cianflone NF, Wallace MR, Looney D. Successful secondary prophylaxis for primary effusion lymphoma with human herpesvirus 8 therapy. *AIDS*. 2006;20(11):1567-1569. Available at http://www.ncbi.nlm.nih.gov/pubmed/16847420.

54. 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(5):589-597. Available at http://www.ncbi.nlm.nih.gov/pubmed/19801945.

55. Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. *AIDS*. 2013;27(10):1603-1613. Available at http://www.ncbi.nlm.nih.gov/pubmed/23462220.

56. Kowalkowski MA, Kramer JR, Richardson PR, Suteria I, Chiao EY. Use of boosted protease inhibitors reduces Kaposi sarcoma incidence among male veterans with HIV infection. *Clin Infect Dis*. 2015;60(9):1405-1414. Available at http://www.ncbi.nlm.nih.gov/pubmed/25586682.

57. Portsmouth S, Stebbing J, Gill J, et al. A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors or protease inhibitors in preventing Kaposi's sarcoma. *AIDS*. 2003;17(11):F17-22. Available at http://www.ncbi.nlm.nih.gov/pubmed/12853764.

58. Gantt S, Cattamanchi A, Krantz E, et al. Reduced human herpesvirus-8 oropharyngeal shedding associated with protease inhibitor-based antiretroviral therapy. *J Clin Virol*. 2014;60(2):127-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/24698158.

59. Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. *J Clin Oncol*. 2005;23(22):5224-5228. Available at http://www.ncbi.nlm.nih.gov/pubmed/16051964.

60. 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(2):150-157. Available at http://www.ncbi.nlm.nih.gov/pubmed/22395672.

61. Martin-Carbonero L, Palacios R, Valencia E, et al. Long-term prognosis of HIV-infected patients with Kaposi sarcoma treated with pegylated liposomal doxorubicin. *Clin Infect Dis*. 2008;47(3):410-417. Available at http://www.ncbi.nlm.nih.gov/pubmed/18582203.

62. Gotti D, Raffetti E, Albini L, et al. Survival in HIV-infected patients after a cancer diagnosis in the ART Era: results of an italian multicenter study. *PLoS One*. 2014;9(4):e94768. Available at http://www.ncbi.nlm.nih.gov/pubmed/24760049.

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020