

## Appendix E. Archived Sections

### Overview

Following the 2021 Rescoping Consultation of the *Guidelines for the Prevention and Treatment of Opportunistic Infections in Children with and Exposed to HIV*, several opportunistic infections were identified as either with low frequency in children and prepubertal adolescents with HIV or without HIV-specific management implications. As a result, these sections were recommended not to be further reviewed by the Panel on Opportunistic Infections in Children with and Exposed to HIV (the Panel). The archived sections are Human Herpesvirus 8 Disease, Influenza, and Progressive Multifocal Leukoencephalopathy.

This appendix provides access to the last updated versions of sections that are no longer being reviewed by the Panel.

- [Human Herpesvirus 8 Disease](#)
- [Influenza](#)
- [Progressive Multifocal Leukoencephalopathy](#)

# Human Herpesvirus 8 Disease

Updated: December 15, 2016

Reviewed: December 15, 2016

Panel's Recommendations	
I.	<p>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?</p> <ul style="list-style-type: none"> <li>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 (<b>strong, very low</b>).</li> </ul>
II.	<p>Among HIV-infected children, does initiation of antiretroviral therapy (ART) (as compared with non-initiation) reduce the risk of Kaposi sarcoma?</p> <ul style="list-style-type: none"> <li>Effective suppression of HIV replication with ART is recommended to reduce the risk of HHV-8-associated Kaposi sarcoma (<b>strong, low</b>).</li> </ul>
III.	<p>For HIV-infected patients initiating ART, are any specific ART regimens associated with lower rates of Kaposi sarcoma?</p> <ul style="list-style-type: none"> <li>Data are insufficient and conflicting upon which to base a recommendation for a particular ART regimen for prevention of Kaposi sarcoma (<b>weak, low</b>).</li> </ul>
IV.	<p>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?</p> <ul style="list-style-type: none"> <li>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 (<b>strong, very low</b>).</li> </ul>
V.	<p>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?</p> <ul style="list-style-type: none"> <li>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 (<b>strong, low</b>). For localized Kaposi sarcoma (stage T0 disease), the benefit of systemic chemotherapy (in addition to ART) is unclear.</li> </ul>
VI.	<p>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?</p> <ul style="list-style-type: none"> <li>For patients with Kaposi-sarcoma-associated IRIS, chemotherapy along with continuation of ART is recommended (<b>strong, low</b>).</li> </ul>
VII.	<p>Among HIV-infected children who achieve remission from Kaposi sarcoma, what therapies are recommended to lower the risk of recurrence?</p> <ul style="list-style-type: none"> <li>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 (<b>strong, low</b>).</li> </ul>
<p><b>Rating System</b></p> <p><i>Strength of Recommendation: Strong; Weak</i></p> <p><i>Quality of Evidence: High; Moderate; Low; or Very Low</i></p>	

## 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 precedes development of the tumors.<sup>1</sup>

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).<sup>2</sup> 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.<sup>3</sup> 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.<sup>3,4</sup> 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.<sup>5-9</sup>

HHV-8 is transmitted through oral and, possibly, genital secretions. Immunocompetent HHV-8-infected adults frequently shed HHV-8 in their oropharyngeal secretions.<sup>10</sup> 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.<sup>11,12</sup> 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.<sup>11-18</sup> HHV-8 can also be transmitted through exposure to infected blood, including through intravenous (IV) drug use and blood product transfusions.<sup>19</sup>

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.<sup>20-22</sup> Iatrogenic KS has emerged as well, predominantly among adults in developed settings, with increasing use of immunosuppressive therapies and organ transplantation.<sup>23</sup> Pediatric cases of iatrogenic KS after liver or bone marrow transplantation have also been described.<sup>24-27</sup>

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<sup>3</sup> in adults). It

should be noted, however, that 5% to 10% of newly diagnosed KS in adults occurs in those with CD4 cell count  $>300/\text{mm}^3$  and/or low or undetectable plasma HIV RNA levels.<sup>28,29</sup>

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.<sup>30-36</sup> 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.<sup>37,38</sup> A more severe illness has been described in immunocompromised patients, who may present with disseminated infection with fever, lymphadenopathy, splenomegaly, and pancytopenia.<sup>39,40</sup> Reactivation of HHV-8 has been associated with hemophagocytic lymphohistiocytosis in HIV-infected adults.<sup>41</sup>

KS presentation varies widely, with cutaneous, oral, lymphatic, or visceral involvement, or some combination of the three.<sup>42,43</sup> Pediatric presentations differ from those of adults and are best described in retrospective cohort studies from sub-Saharan Africa.<sup>21,43-45</sup> Cutaneous forms involve characteristic non-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  $\geq 90\%$  and interassay agreement is poor.<sup>46</sup> 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 coinfectd.<sup>47</sup> 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.<sup>48</sup> 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.<sup>49,50</sup>

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.<sup>50</sup> IV ganciclovir or oral valganciclovir may be considered for treating multicentric Castleman disease<sup>51</sup> and may be a useful adjunct for treating primary effusion lymphoma.<sup>52,53</sup> 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.<sup>54</sup> 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.<sup>55</sup>

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 coinfecting individuals will develop KS. Seroprevalence of HHV-8 varies by country, but in some areas reaches  $\geq 50\%$  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.<sup>56,57</sup> 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.<sup>45</sup>

#### **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 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.<sup>58</sup> 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.<sup>56,57</sup> 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<sup>3</sup>.<sup>28,29</sup>

## ***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.<sup>21,44,58</sup>

### **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.<sup>44,45,58</sup> 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.<sup>59</sup> 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.<sup>55,60</sup>

## ***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)**.

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.<sup>61</sup> In 1 large Italian study, a multivariate analysis demonstrated a strong association between use of ART and increased 10-year survival rates after KS.<sup>62</sup>



## 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 and its 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](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, Mauclore 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/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/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, Nicastrì 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. *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-naïve 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>.



# Influenza

Updated: July 26, 2018

Reviewed: July 26, 2018

Panel's Recommendations	
I.	<p><b>Does influenza vaccination of children with HIV and their contacts decrease incidence or severity of influenza (compared with no vaccination)?</b></p> <ul style="list-style-type: none"> <li>The prevention of influenza in children with HIV aged <math>\geq 6</math> months should include annual administration of inactivated influenza vaccine (either quadrivalent or trivalent, depending on availability) (<b>strong, moderate</b>).</li> <li>Currently, it is suggested that children with HIV not receive live-attenuated influenza vaccine<sup>a</sup> (e.g., intranasal administered influenza vaccine, FluMist) (<b>weak, very low</b>).</li> <li>Household members and close contacts (aged <math>\geq 6</math> months) of children with HIV should receive yearly influenza vaccine (any recommended and otherwise medically appropriate influenza vaccine) (<b>strong, moderate</b>).</li> </ul>
II.	<p><b>Does pre- or post-exposure antiviral chemoprophylaxis against influenza with a neuraminidase inhibitor in children with HIV prevent influenza and/or reduce morbidity (compared with no chemoprophylaxis)?</b></p> <ul style="list-style-type: none"> <li>Pre-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza may be considered in children with HIV with severe immunosuppression (i.e., CD4 T lymphocyte [CD4] cell percentage <math>&lt;15\%</math>) while influenza virus is circulating in the community, after careful consideration of risks and benefits as outlined in Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) and Infectious Diseases Society of America (IDSA) guidelines (<b>weak, low</b>).</li> <li>Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with severe immunosuppression (i.e., CD4 percentage <math>&lt;15\%</math>), regardless of influenza vaccination status, if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza (<b>strong, moderate</b>).</li> <li>Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with moderate to no immunosuppression in whom influenza vaccination is contraindicated or unavailable (<b>strong, moderate</b>) or in seasons in which low influenza vaccine effectiveness is documented (<b>strong, low</b>), if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza.</li> </ul>
III.	<p><b>Does antiviral treatment of children with HIV with diagnosed influenza decrease severity, morbidity, or complications of influenza (compared with no treatment)?</b></p> <ul style="list-style-type: none"> <li>Children with HIV requiring hospitalization for laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible according to CDC/ACIP and IDSA guidelines. When influenza is suspected in the hospital setting, empiric antiviral treatment should be given without waiting for confirmatory laboratory testing and without regard to illness duration (<b>strong, moderate</b>). Antiviral treatment may provide benefit when started after 48 hours of illness onset in patients with severe, complicated, or progressive illness, and in hospitalized patients (<b>weak, low</b>).</li> <li>Children with HIV in the outpatient setting with laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible (<b>strong, moderate</b>). Treatment should be initiated as early as possible regardless of influenza vaccine status and regardless of illness severity according to CDC/ACIP and IDSA guidelines.</li> <li>In the outpatient setting, consideration could be given to withholding treatment if symptom duration exceeds 48 hours, the child has no HIV viremia or evidence of immunosuppression, is aged <math>&gt;5</math> years, and has no other underlying condition that places the child at high risk of complications from influenza (<b>weak, low</b>).</li> </ul>

### Rating System

Strength of Recommendation: Strong; Weak

Quality of Evidence: High; Moderate; Low; or Very Low

<sup>a</sup> As of the 2017–2018 influenza season, live attenuated influenza vaccine (LAIV) **is not recommended** by ACIP for any pediatric or adult patient given concerns about effectiveness. Please see the most recent ACIP statements regarding use of LAIV in future seasons.

## Epidemiology

Influenza viruses are spread directly from person to person across distances up to 6 feet via large or small droplets generated by coughing or sneezing, or indirectly from contaminated surfaces to hands to mucosal membranes.<sup>1</sup> Influenza has an incubation period of 1 to 4 days (mean: 2 days),<sup>2</sup> and can be shed by adults from 1 day before to 5 to 7 days after onset of symptoms and by children from several days before to  $\geq 10$  days after illness onset.<sup>3</sup> Viral shedding can occur over longer periods in those with chronic diseases, including patients with immunosuppression or those receiving systemic corticosteroid therapy.<sup>4–7</sup>

Seasonal influenza viruses can be divided into three types: A, B, and C. Influenza A viruses are further subdivided based on surface glycoproteins: hemagglutinin (H) and neuraminidase (N). Influenza A viruses circulate primarily among aquatic birds, but also among humans and other animals, including pigs, horses, and seals. Influenza A virus subtypes H1N1pdm09 and H3N2 currently circulate among humans. Influenza B viruses circulate primarily among humans.<sup>8</sup> Influenza C viruses circulate primarily among animals such as swine and dogs but are increasingly appreciated in humans.<sup>9–12</sup> Influenza A and B, but not C, cause seasonal outbreaks. Surveillance and immunization are currently performed for influenza A and B. Two influenza A subtypes (one H1N1 and one H3N2); and one influenza B strain for trivalent vaccine formulations, or two influenza B strains for quadrivalent vaccine formulations are included in current seasonal influenza vaccines. In the United States, influenza viruses cause annual outbreaks lasting from winter through spring.

The Centers for Disease Control and Prevention (CDC) has identified certain groups to be at risk of complications from influenza, including individuals with immunosuppression caused by HIV infection.<sup>13</sup> The burden of influenza virus in children with HIV has been characterized in limited case reports and case series, but assessment of its impact has been confounded by the stage of HIV infection, type of antiretroviral therapy (ART), and other comorbidities.<sup>14</sup> In the era before the availability of combination antiretroviral therapy (cART), multiple large epidemiological studies suggested high hospitalization and mortality rates associated with influenza in individuals with HIV.<sup>15,16</sup> However, observations reported during the cART era suggest that better control of HIV infection is associated with a milder course of influenza. In an outbreak of pandemic 2009 H1N1 influenza in Germany involving 15 schoolchildren with HIV receiving cART, the clinical course of influenza in children with HIV was similar to that in children without HIV.<sup>17</sup> A case series of 13 children with HIV with pandemic 2009 H1N1 in Barcelona in 2009 also reported outcomes similar to those in groups without HIV.<sup>18</sup> In both reports, half of the children were aged  $<13$  years, had CD4 T lymphocyte (CD4) counts  $>500$  cells/mm<sup>3</sup>, and had very low or undetectable HIV viral loads. Recent adult data suggest that, despite the introduction of ART, influenza-related mortality in adults with AIDS is still greater than in the general population.<sup>19</sup> Further, using national mortality and laboratory surveillance data from 1998–2009, a study from South Africa reported that the risk of death associated with influenza in children aged  $<5$  years was greater in children with HIV than in



those without HIV (RR 11.5, 95% CI, 9.6–12.6).<sup>20</sup> Large prospective, observational studies of children with HIV are needed to further substantiate these findings.

## Clinical Manifestations

Signs and symptoms related to influenza are similar in children with and without HIV and include fever, cough, and rhinorrhea in the majority of patients.<sup>17,18,21</sup> Loss of appetite was more common in patients with HIV than in patients without HIV in one study.<sup>22</sup> In a prospective cohort study of hospitalized children with laboratory-confirmed influenza conducted in South Africa from 1997 to 1999, prior to cART availability, radiographic evidence of alveolar consolidation was more frequent in children with HIV than in children without HIV. Clinical outcomes including duration of hospitalization and in-hospital mortality were similar for both children with and without HIV.<sup>22</sup> In one small study conducted during the 2009 H1N1 pandemic, chest radiography patterns differed with HIV status; children with HIV were more likely to have an interstitial infiltrate and children without HIV more likely to have a consolidative infiltrate. Children with HIV were also more likely to have leukopenia associated with their influenza diagnosis than children without HIV.<sup>23</sup>

## Diagnosis

The laboratory approach to diagnosis of influenza in children with and without HIV is identical. This includes rapid influenza diagnostic tests (RIDTs), immunofluorescence assays, reverse transcription-polymerase chain reaction (RT-PCR) assays, and viral culture. RT-PCR and viral culture are considered the gold standard influenza tests. Viral culture has lower sensitivity than RT-PCR and results are not immediately available. RIDTs offer point-of-care diagnosis, but sensitivity is substantially lower than for viral culture or RT-PCR, which makes false-negative results a significant concern in clinical application. In addition RIDTs can be falsely positive when the prevalence of influenza is low, thus limiting their reliability for patient management in both high and low prevalence seasons.<sup>24</sup> Clinical diagnosis with laboratory confirmation of influenza is important, especially for hospitalized patients and outpatients at higher risk of influenza complications. Molecular diagnostic methods (e.g., RT-PCR) offer the most sensitive and specific diagnostic testing and can be performed at many specialized laboratories, such as hospital laboratories, commercial referral laboratories, and county and state public health laboratories.

## Prevention Recommendations

### *Preventing Exposure*

Basic personal hygiene, including hand hygiene and proper cough etiquette, are mainstays of influenza prevention. Individuals should avoid touching their eyes, nose, and mouth and avoid contact with sick individuals. Hands should be washed often with soap and water or, if soap and water are unavailable, with an alcohol-based hand rub containing at least 60% alcohol. Proper hand washing technique involves wetting hands with clean running water, applying soap, and rubbing and scrubbing all hand surfaces and under the fingernails for at least 20 seconds. Hands should be dried with a clean towel or air dried. When using alcohol-based hand rub, the hand rub should be applied to one hand, and the hands (including all hand surfaces and fingers) should be rubbed together until dry.

Cough etiquette directs that individuals cough or sneeze into a tissue rather than into their hands. A soiled tissue should be disposed of in a waste basket. Measures used by public health authorities

during influenza pandemics include recommendations to reduce crowding, to maintain a few feet of distance from others, to avoid shaking hands or hugging at gatherings, and to avoid gatherings altogether (see [Preventing the Flu: Good Health Habits Can Help Stop Germs](#) and [Handwashing: Clean Hands Save Lives](#)).

Prolonged influenza viral replication in immunocompromised patients has implications for spread of influenza in the health care setting, as well as in the community. Immunocompromised patients with prolonged viral replication in the respiratory tract could potentially serve as a reservoir for spread of influenza in the hospital and the community. In addition, prolonged viral replication increases the risk for emergence of antiviral resistance if antiviral exposure occurs. Strategies to prevent the spread of influenza in health care facilities include use of standard and droplet precautions by health care workers, as well as caution when performing aerosol-generating procedures according to [Healthcare Infection Control Practices Advisory Committee guidelines](#).<sup>25</sup>

In addition to the above measures, influenza prevention efforts for children with HIV also include vaccinating the children's close contacts and limiting spread of influenza from household members. Household members may be vaccinated with any medically appropriate vaccine formulation. Though not recommended for the 2017–2018 season, live attenuated influenza vaccine (LAIV) is considered safe for household contacts of children with HIV if the contacts fulfill criteria for LAIV receipt. Isolation of household members with any acute respiratory illness from the child with HIV, prompt influenza testing, and presumptive antiviral treatment in potentially infected household members are additional tools to prevent spread of influenza to children with HIV.

### ***Preventing First Episode of Disease***

Annual influenza vaccination is a cornerstone of influenza prevention at both the individual and community level.<sup>26</sup> Past concerns about an increase in HIV viral load following influenza vaccination have not been substantiated, particularly in individuals on ART.<sup>13,27-31</sup> Currently in the United States, inactivated influenza vaccine (IIV) is recommended for patients with HIV according to the CDC Advisory Committee on Immunization Practices (ACIP) guidelines. Studies examining the immune response of children and adolescents with HIV on ART to inactivated influenza vaccination have generally shown immune responses comparable to those seen in individuals without HIV.<sup>32</sup> Children with HIV-related immunologic impairment or with symptomatic HIV demonstrate decreased immune responses to influenza vaccination (see Recommendation Table). High-dose IIV was recently studied in a small cohort of children and young adults with HIV, though it was not significantly more immunogenic in these patients than standard-dose IIV.<sup>33</sup> Additional studies of high-dose IIV in populations at increased risk for influenza are in progress. LAIV is **not recommended** for immunosuppressed persons per CDC/ACIP guidance.<sup>34</sup> Furthermore, current Infectious Diseases Society of America (IDSA) guidelines for LAIV immunization of immunocompromised persons state that LAIV **should not be administered** to immunocompromised persons or persons with HIV.<sup>35</sup> Some experts would consider using LAIV (which may remain available) in children with HIV on ART without CD4-defined immunosuppression on the basis of demonstrated safety and immunogenicity in children with HIV who meet these conditions.<sup>36</sup> However, the CDC/ACIP and IDSA guidelines recommend against such practice, and LAIV is not licensed for use in children with HIV. Further, LAIV is not currently recommended by ACIP for all populations because of decreased effectiveness.

Contraindications to the use of inactivated influenza vaccines are few and are the same for individuals with and without HIV. Influenza vaccines **are not approved** for children aged

<6 months. Per CDC/ACIP guidance, persons with a previous severe allergic reaction to influenza vaccine **should not receive influenza vaccine in the future.**<sup>34</sup> Future avoidance of influenza vaccine in this setting is recommended regardless of the component suspected of being responsible for the reaction. Persons who report having had egg-associated reactions involving symptoms other than hives (e.g., angioedema, respiratory distress, lightheadedness, or recurrent emesis) or who required epinephrine or another emergency medical intervention, may receive any licensed and recommended influenza vaccine “that is otherwise appropriate for the recipient’s age and health status.”<sup>34</sup> In persons with severe egg reactions, influenza vaccine should be administered in an inpatient or outpatient medical setting with supervision by a health care provider able to recognize and manage severe allergic conditions.<sup>34</sup> A physician should be consulted before influenza vaccine is administered to children who have a moderate-to-severe illness with a fever (in which case, vaccination should be postponed until the child recovers).

Options for antiviral chemoprophylaxis of influenza include antiviral administration in the pre- or post-exposure setting to children and adolescents with HIV (see Panel Recommendations above). Pre-exposure prophylaxis should rarely be used, except in persons who are severely immunocompromised and therefore at very high risk for influenza virus-associated morbidity and mortality during periods of greatly increased risk for influenza exposure.<sup>37</sup> The choice to provide post-exposure prophylaxis to an individual patient depends on the patient’s state of immunosuppression and immunization status, as well as the seasonal vaccine effectiveness depending on the vaccine match with the circulating strains of influenza (See Panel Recommendations above and Evidence Summary below).<sup>37</sup> Selection of an antiviral drug for chemoprophylaxis should be based on current CDC/ACIP influenza antiviral recommendations and take into consideration the weekly antiviral susceptibility testing data for the circulating influenza virus strains that is provided by CDC (see [Weekly U.S. Influenza Surveillance Report](#) or [FluView](#)). Post-exposure antiviral chemoprophylaxis should be started within 48 hours of exposure to a contact with confirmed or suspected influenza. Oseltamivir and zanamivir, which are members of the antiviral class of medications called neuraminidase inhibitors, are approved and are recommended for chemoprophylaxis against influenza A and B viruses in children. Oseltamivir prophylaxis is not Food and Drug Administration (FDA)-approved for children aged <1 year, but the American Academy of Pediatrics (AAP) and CDC have issued recommendations for prophylaxis of children aged ≥3 months; zanamivir prophylaxis is not recommended for children aged <5 years (see table below). Although oseltamivir resistance has been documented previously among circulating seasonal influenza A (H1N1) virus strains during the 2008–2009 influenza season, since September 2009, most (99%) circulating influenza A and B viruses have been susceptible to oseltamivir.<sup>37,38</sup> Amantadine and rimantadine, adamantane derivatives which only have activity against influenza A viruses, are approved but not currently recommended for chemoprophylaxis of influenza A virus infection because of widespread resistance of current influenza A (H3N2 and H1N1pdm09) virus strains to adamantanes.<sup>37,39</sup>

### ***Discontinuing Primary Prophylaxis***

Though used only rarely, when a pre-exposure chemoprophylaxis strategy is employed, antiviral chemoprophylaxis should continue for the duration of influenza virus circulation in the community.<sup>37</sup>

The recommended duration of post-exposure chemoprophylaxis depends on the type of exposure, whether influenza vaccination was provided after the exposure, and whether influenza vaccine is anticipated to be effective based on the child’s degree of immunosuppression and the degree of match with circulating influenza viruses.<sup>37,40</sup> If influenza vaccination is provided after contact,

chemoprophylaxis duration should generally be 2 weeks after vaccination. If exposure is to a household contact, chemoprophylaxis duration should be 7 days (see [Influenza Antiviral Medications: Summary for Clinicians](#)). If chemoprophylaxis is provided in setting of an institutional outbreak, the duration is either 14 days, or 7 days after onset of symptoms in the last person infected, whichever is longer. The duration of chemoprophylaxis after other exposure types should generally be 7 days.

## Treatment Recommendations

### *Treating Disease*

Treatment of influenza in children with HIV is recommended according to CDC/ACIP guidelines. The recommended duration of treatment is 5 days, but may need to be extended in severely ill hospitalized or immunocompromised patients.<sup>40-43</sup> As with primary chemoprophylaxis, selection of an antiviral drug for treatment should be based on current CDC/ACIP influenza antiviral recommendations and should account for antiviral susceptibility testing data for circulating influenza virus strains that is provided by CDC (see [Weekly U.S. Influenza Surveillance Report](#) or [FluView](#)). Currently recommended influenza antiviral medications are the neuraminidase inhibitor drugs, oseltamivir (orally administered), zanamivir (inhaled), and peramivir (intravenous). Peramivir is approved for treatment in persons aged  $\geq 18$  years. All three are effective for treatment against influenza A and B viruses. Oseltamivir is FDA-approved for treatment of influenza in children aged  $\geq 2$  weeks; however, both CDC and AAP recommend the use of oral oseltamivir for treatment of influenza in infants aged  $< 2$  weeks when needed (see [Influenza Antiviral Medications: Summary for Clinicians](#)).<sup>43</sup>

Although oseltamivir resistance was documented in circulating seasonal influenza A (H1N1) virus strains during the 2008–2009 influenza season, since September 2009, most (99%) of circulating influenza A and B viruses have been susceptible to oseltamivir.<sup>37,38</sup> Zanamivir is approved for treatment of influenza in children aged  $\geq 7$  years (see Table below). Peramivir, though FDA-approved only for treatment of persons aged  $\geq 18$  years, has been studied in pediatric populations.<sup>44-46</sup> Importantly, the most common neuraminidase inhibitor mutation (H275Y) imparts resistance to both oseltamivir and peramivir.<sup>47,48</sup> Adamantanes (rimantadine, amantadine) have activity only against influenza A viruses, but are not currently recommended for treatment of influenza A because of resistance of currently circulating influenza A (H3N2 and H1N1pdm09 virus strains).<sup>37,39</sup>

### *Monitoring of Adverse Events*

Clinicians should take into account patients' age, weight, renal function, history of seizures, level of immunosuppression, other medical conditions, and potential drug interactions when considering administration of influenza antiviral medications and evaluating their associated adverse events.<sup>37</sup>

### **Oseltamivir**

In studies in adults and children, mild nausea and vomiting have been the most common side effects of treatment with oseltamivir;<sup>49,50</sup> however, these symptoms can be reduced if the medication is taken with food.<sup>51</sup> Despite earlier post-market reports from Japan of transient neuropsychiatric events manifested as self-injury or delirium, oseltamivir has not been reproducibly associated with increased risk of neuropsychiatric events.<sup>52</sup> Moreover, influenza infection itself is associated with neurologic complications such as febrile seizures, encephalopathy, and encephalitis. FDA recommends close

monitoring for abnormal behavior in patients treated with oseltamivir.<sup>51</sup> FDA and CDC also recommend that clinicians and pharmacists pay careful attention to avoid dosing errors in young children.<sup>53</sup>

## **Zanamivir**

Because of cases of respiratory deterioration manifested as decreased forced expiratory volume or bronchospasm in patients with asthma or chronic obstructive pulmonary disease receiving zanamivir, this agent **is not recommended** for treatment of influenza in patients with underlying pulmonary disease. In clinical treatment studies involving patients with uncomplicated influenza, common adverse events were similar in those treated with inhaled zanamivir and those treated with inhaled placebo.<sup>37,41</sup>

## **Drug Interactions**

Clinical data are limited with respect to drug interactions between influenza antiviral drugs and antiretroviral (ARV) drugs, and no clinical trials to date have evaluated the safety or efficacy of using combinations of different classes of influenza antiviral drugs.<sup>37</sup> However, information derived from pharmacology and pharmacokinetic studies of oseltamivir suggests that clinically significant drug interactions with ARV agents are unlikely. Moreover, since none of the neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) affect cytochrome P450 (CYP450) isoenzymes, no clinically significant drug interactions are predicted based on *in vitro* studies.

## ***Managing Treatment Failure (Influenza Disease Progression)***

Clinicians developing management plans in response to treatment failure or severe illness associated with influenza viral infections can consider changing antiviral dosing or route of administration, increasing duration of therapy, or tailoring therapy based on viral resistance.<sup>40</sup> The potential use of increased oseltamivir doses in critically ill patients has emerged from concerns surrounding enteric absorption of oseltamivir in this patient population, but these concerns have not been substantiated in clinical trials. One small study demonstrated therapeutic plasma levels of oseltamivir in critically ill adult patients comparable to those seen in ambulatory adult patients.<sup>54</sup> In addition, a prospective study from Hong Kong showed no overall clinical or virologic benefit of higher dose as compared to standard dose oseltamivir in hospitalized adults, though a trend to more rapid viral clearance of influenza B, but not of influenza A, was noted in a sub-analysis.<sup>55</sup> Patients who are severely ill and hospitalized or who are immunosuppressed may require longer treatment with oseltamivir.<sup>40</sup> For hospitalized children or those with severe disease, treatment with inhaled zanamivir is not recommended because evidence for its use in this setting is lacking. In December 2014, FDA approved intravenous (IV) peramivir for treatment of acute uncomplicated influenza in persons aged  $\geq 18$  years. Although not licensed for children, pediatric use of peramivir is reported and off-label use could be considered in severely ill children, especially those patients who cannot tolerate or absorb oral/enteral oseltamivir. Expert opinion supports consideration of IV peramivir use in hospitalized children aged  $\geq 2$  years and adults or those with severe disease, although efficacy in this setting has not been demonstrated.<sup>40,44</sup> Further studies to support its safety and efficacy are needed.<sup>45,56,57</sup>

Prior to the 2017–2018 influenza season, IV zanamivir was available through clinical trial enrollment or via an Emergency Investigational New Drug application for settings in which oseltamivir-resistant influenza virus infection was suspected or confirmed (see [Influenza Antiviral Medications: Summary for Clinicians](#)). However, at present IV zanamivir is no longer available in the United States.



Importantly, as noted above, if oseltamivir-resistant influenza virus infection is suspected or confirmed, peramivir is not indicated because of demonstrated cross-resistance between oseltamivir and peramivir.

## Preventing Recurrence

See sections Preventing Exposure and Preventing First Episode of Disease.

## Discontinuing Secondary Prophylaxis

Not applicable.

## Primary Prevention

### *1. Does influenza vaccination of children with HIV and their contacts decrease incidence or severity of influenza (compared with no vaccination)?*

- i. Prevention of influenza in children with HIV aged  $\geq 6$  months should include annual administration of inactivated influenza vaccine (either quadrivalent or trivalent, depending on availability) (**strong, moderate**). This recommendation is based on review of IDSA,<sup>35</sup> CDC/ACIP,<sup>34</sup> and AAP<sup>43</sup> guidelines.

Annual influenza vaccination is universally recommended for all children aged  $\geq 6$  months.<sup>34</sup> Studies of influenza vaccination in children with HIV have generally shown that influenza vaccination is safe and immunogenic. Some studies have demonstrated that, compared to children without HIV, children with HIV have decreased antibody responses to influenza vaccination.<sup>58,59,60,61</sup> Others have shown that children with HIV with greater immune impairment or a more symptomatic clinical stage had decreased immune response to influenza vaccination.<sup>62,63</sup> Despite this potential for modestly impaired immune response to influenza vaccination in children with HIV, seroprotection (i.e., hemagglutination inhibition [HAI] antibody titer  $\geq 1:40$ ) was achieved in up to 92% of vaccine recipients<sup>64</sup> and seroconversion ( $\geq 4$ -fold rise in post-vaccine HAI titer as compared to pre-vaccine HAI titer) in as many as 85% of vaccine recipients<sup>65</sup> in studies of children with HIV.

In one randomized, double-blind, placebo controlled trial of influenza vaccination in children with HIV, immune responses were measured by HAI and vaccine efficacy was determined using active surveillance data.<sup>66</sup> Seroprotection among the vaccinated population was low and vaccine efficacy was only 17.7% (95% CI, 0% to 62.5%). Importantly, 92% of participants in this study were receiving ART and the median CD4 percentage was 33.5 (range: 15.2% to 55.9%). However, in a similar study performed in adults with HIV in the same setting, vaccine efficacy was 75.5% (95% CI, 9.2% to 95.6%).<sup>67</sup> Thus, given the CDC/ACIP recommendation for universal influenza vaccination in children aged  $\geq 6$  months and the potential for protection against influenza by administration of influenza vaccination, yearly administration of influenza vaccine to children with HIV is strongly advised.

- ii. Currently, it is suggested that children with HIV not receive live-attenuated influenza vaccines (intranasal administered influenza vaccine, FluMist) (**weak, very low**). This recommendation is based on review of the IDSA guideline for vaccination in the immunocompromised host.<sup>35</sup>

Several studies have evaluated LAIV administration to children and/or adults with HIV.<sup>68,36,69,60,70</sup> In these studies, LAIV administration was safe and not associated with serious adverse events. In most of these studies, individuals with HIV were not significantly immunocompromised at the time of study vaccination. Although some experts would consider using LAIV in children with HIV on ART without CD4-defined immunosuppression on the basis of demonstrated safety and immunogenicity in children with HIV meeting these conditions,<sup>36</sup> current IDSA guidelines for immunization of immunocompromised hosts recommend against immunization of children, adolescents, and adults with HIV with LAIV.<sup>35</sup>

- iii. Household members and close contacts (aged  $\geq 6$  months) of children with HIV should receive yearly influenza vaccine (any recommended and otherwise medically appropriate influenza vaccine) (**strong, moderate**).

Annual influenza vaccination is universally recommended for all adults and children aged  $\geq 6$  months.<sup>34,71</sup> Given the immunocompromised state of children with HIV and the potential for impaired immune response to influenza vaccination, special emphasis on vaccination of those persons in household and/or close contact with children with HIV is warranted. Ensuring that household/close contacts are vaccinated against influenza likely provides additional prevention against influenza in children with HIV. While there are no specific studies addressing a “cocoon” strategy for influenza prevention in children with HIV, this recommendation is in accordance with universal influenza vaccination recommended by CDC/ACIP.

## ***2. Does pre- or post-exposure antiviral chemoprophylaxis against influenza with a neuraminidase inhibitor in children with HIV prevent influenza and/or reduce morbidity (compared with no chemoprophylaxis)?***

- i. Pre-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza may be considered in children with HIV with severe immunosuppression (i.e., CD4 percentage  $< 15\%$ ) while influenza virus is circulating in the community (**weak, low**). Use of this strategy requires careful consideration of risks and benefits and attention to influenza circulation as outlined in CDC/ACIP,<sup>37</sup> IDSA,<sup>42</sup> and AAP<sup>43</sup> guidelines.
- ii. Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with severe immunosuppression (i.e., CD4 percentage  $< 15\%$ ) regardless of influenza vaccination status, if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza (**strong, moderate**).
- iii. Post-exposure antiviral chemoprophylaxis with a neuraminidase inhibitor against influenza is recommended in children with HIV with moderate to no immunosuppression in whom influenza vaccination is contraindicated or unavailable (**strong, moderate**) or in seasons in which low influenza vaccine effectiveness is documented (**strong, low**) if antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza.

No antiviral chemoprophylaxis studies for prevention of influenza have been specifically performed in children with HIV. These recommendations were made with reference to

current guidelines on antiviral chemoprophylaxis against influenza published by the CDC/ACIP, IDSA, and AAP. In severely immunosuppressed children, influenza vaccination may be poorly immunogenic. Therefore, antiviral chemoprophylaxis may be considered for children with HIV with severe immunosuppression regardless of vaccination status.

Post-exposure antiviral chemoprophylaxis should be given **only** if it can be started within 48 hours after the initial exposure **and** if the recipient is asymptomatic. If more than 48 hours have elapsed since the initial exposure, then either no chemoprophylaxis should be given, or the treatment antiviral dose should be given. If the potential recipient is already symptomatic, prompt antiviral treatment should be initiated (see Clinical Question #3). Use of prophylactic once-daily dosing in the setting of active viral replication poses a risk of emergence of antiviral resistance.<sup>72-75</sup> Further information regarding antiviral chemoprophylaxis can be found at [Influenza Antiviral Medications: Summary for Clinicians](#).

## Treatment

### 3. *Does antiviral treatment of children with HIV with diagnosed influenza decrease severity, morbidity, or complications of influenza (compared with no treatment)?*

- i. Children with HIV requiring hospitalization for laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible according to CDC/ACIP and IDSA guidelines. When influenza is suspected in the hospital setting, empiric antiviral treatment should be given without waiting for confirmatory laboratory testing and without regard to illness duration (**strong, moderate**). Antiviral treatment may provide benefit when started after 48 hours of illness onset in patients with severe, complicated, or progressive illness, and in hospitalized patients (**weak, low**).
- ii. Children with HIV in the outpatient setting with laboratory-confirmed or clinically suspected influenza should receive antiviral treatment as soon as possible (**strong, moderate**). Treatment should be initiated as early as possible regardless of influenza vaccine status and regardless of illness severity according to CDC/ACIP and IDSA guidelines.
- iii. In the outpatient setting, consideration could be given to withholding treatment if symptom duration exceeds 48 hours, the child has no HIV viremia or evidence of immunosuppression, is aged >5 years, and has no other underlying condition that places the child at high risk of complications from influenza (**weak, low**).

No antiviral treatment studies have been specifically performed in children with HIV with influenza. The recommendations are made with reference to current influenza chemoprophylaxis and treatment guidelines published by CDC/ACIP,<sup>37</sup> IDSA,<sup>42</sup> and AAP.<sup>43</sup> Further information regarding antiviral treatment can be found at [Influenza Antiviral Medications: Summary for Clinicians](#).

## Secondary Prevention

Not applicable.



## Dosing Recommendations for Chemoprophylaxis and Treatment of Influenza

Indication	First Choice	Alternative	Comments/Special Issues
<b>Primary Chemoprophylaxis (Pre- and Post-Exposure)</b>  <b>Influenza A and B</b>	<b>Oseltamivir</b> <ul style="list-style-type: none"> <li>Aged &lt;3 Months: Not recommended<sup>a</sup></li> <li>Aged 3 Months to &lt;1 Year: Oseltamivir 3mg/kg body weight/dose once daily<sup>a</sup></li> <li>Aged ≥1 to 12 Years: Weight-band dosing<sup>a</sup> <ul style="list-style-type: none"> <li>Weighing ≤15 kg: Oseltamivir 30 mg once daily</li> <li>Weighing &gt;15 kg to 23 kg: Oseltamivir 45 mg once daily</li> <li>Weighing &gt;23 kg to 40 kg: Oseltamivir 60 mg once daily</li> <li>Weighing &gt;40 kg: Oseltamivir 75 mg once daily</li> </ul> </li> <li>Aged ≥13 Years: Oseltamivir 75 mg once daily</li> </ul> <b>Zanamivir (Aged ≥5 Years)</b> <ul style="list-style-type: none"> <li>Zanamivir 10 mg (2 inhalations) once daily<sup>b</sup></li> </ul>	None	<b>Pre-Exposure Chemoprophylaxis</b>  <i>Indications</i> <ul style="list-style-type: none"> <li>After careful consideration of risks and benefits, pre-exposure antiviral chemoprophylaxis may be considered for children with HIV with severe immunosuppression while influenza virus is circulating in the community.</li> </ul> <i>Duration</i> <ul style="list-style-type: none"> <li>When employed, pre-exposure antiviral chemoprophylaxis should continue for the duration of influenza virus circulation in the community.</li> </ul> <b>Post-Exposure Chemoprophylaxis</b>  <i>Indications Recommended For:</i> <ul style="list-style-type: none"> <li>Children with HIV with severe immunosuppression regardless of influenza vaccination status.</li> <li>Children with HIV with moderate to no immunosuppression if               <ul style="list-style-type: none"> <li>Influenza vaccination is contraindicated or unavailable; <i>or</i></li> <li>Low influenza vaccine effectiveness is documented in the current influenza season; <i>and</i></li> <li>Antiviral chemoprophylaxis can be started within 48 hours of exposure to an ill person with confirmed or suspected influenza.</li> </ul> </li> </ul> <i>Duration</i>  <b>Note:</b> Duration of chemoprophylaxis depends on the type of exposure, whether influenza vaccination was provided after the exposure, and whether influenza vaccine is anticipated to be effective based on the child's degree of immunosuppression and the degree of match with circulating influenza viruses. <ul style="list-style-type: none"> <li>If influenza vaccination is provided after contact, chemoprophylaxis duration should be 2 weeks after vaccination.</li> </ul>

			<ul style="list-style-type: none"> <li>• If exposure is to a household contact, chemoprophylaxis duration should be 7 days.</li> <li>• If chemoprophylaxis is provided in setting of an institutional outbreak, the duration is either 14 days or 7 days after onset of symptoms in the last person infected, whichever is longer.<sup>c</sup></li> </ul> <p><b>Oseltamivir Dosing Adjustments</b></p> <p><i>Premature Infants</i></p> <ul style="list-style-type: none"> <li>• Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery &lt;38 weeks).<sup>d</sup></li> </ul> <p><i>Renal Insufficiency</i></p> <ul style="list-style-type: none"> <li>• A reduction in dose of oseltamivir is recommended for patients with CrCl &lt;30 mL/min. For patients with CrCl 10–30mL/min, a reduction in chemoprophylaxis dosing frequency to every other day is recommended. Pharmacokinetic data are limited for dosing recommendations for patients with severe renal insufficiency on dialysis.</li> </ul>
<b>Secondary Chemoprophylaxis</b>	N/A	N/A	No role for secondary chemoprophylaxis
<b>Treatment</b> <b>Influenza A and B</b>	<p><b>Oseltamivir<sup>e</sup></b></p> <ul style="list-style-type: none"> <li>• Aged &lt;3 Months: Oseltamivir 3mg/kg/dose twice daily</li> <li>• Aged 3 Months to &lt;1 Year: Oseltamivir 3 mg/kg/dose twice daily</li> <li>• Aged ≥1 to 12 Years: Weight-band dosing <ul style="list-style-type: none"> <li>○ Weighing ≤15 kg: Oseltamivir 30 mg twice daily</li> <li>○ Weighing &gt;15 kg to 23 kg: Oseltamivir 45 mg twice daily</li> <li>○ Weighing &gt;23 kg to 40 kg: Oseltamivir 60 mg twice daily</li> </ul> </li> </ul>	None	<p><i>Duration</i></p> <ul style="list-style-type: none"> <li>• The recommended antiviral treatment duration for either oseltamivir or zanamivir is 5 days. Per CDC recommendations, longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.<sup>c</sup></li> </ul> <p><b>Oseltamivir Dosing Adjustments</b></p> <p><i>Premature Infants</i></p> <ul style="list-style-type: none"> <li>• Current weight-based dosing recommendations for oseltamivir are not appropriate for premature infants (i.e., gestational age at delivery &lt;38 weeks).<sup>d</sup></li> </ul> <p><i>Renal Insufficiency</i></p> <ul style="list-style-type: none"> <li>• Oseltamivir renal dosing is not well established for pediatric patients. For children &gt;40 kg, adult renal dosing can be used.</li> </ul>

	<ul style="list-style-type: none"> <li>○ Weighing &gt;40 kg: Oseltamivir 75 mg twice daily</li> <li>● Aged ≥13 Years: Oseltamivir 75 mg twice daily</li> </ul> <p><b>Zanamivir (Aged ≥7 Years)</b></p> <ul style="list-style-type: none"> <li>● Zanamivir 10 mg (2 inhalations) twice daily<sup>f</sup></li> </ul>		<p><b>CrCl/Dose</b></p> <ul style="list-style-type: none"> <li>● 61–90 mL/minute: 75 mg twice daily</li> <li>● 31–60 mL/minute: 30 mg twice daily</li> <li>● 11–30 mL/minute: 30 mg once daily</li> <li>● ≤10 mL/minute, ESRD on hemodialysis: 30 mg dose after every hemodialysis cycle</li> <li>● ≤10 mL/minute, ESRD continuous ambulatory peritoneal dialysis: single 30 mg dose administered after a dialysis exchange</li> </ul>
--	--	--	--

<sup>a</sup> Oseltamivir is FDA-approved for prophylaxis of influenza in children aged ≥1 year. It is not approved for prophylaxis in children aged <1 year. However, CDC recommends that health care providers who treat children aged ≥3 months to <1 year administer a chemoprophylaxis dose of oseltamivir 3 mg/kg body weight/dose once daily. Chemoprophylaxis for infants aged <3 months is **not recommended** unless the exposure situation is judged to be critical.

<sup>b</sup> Zanamivir **is not recommended** for chemoprophylaxis in children aged <5 years or for children with underlying respiratory disease.

<sup>c</sup> See Fiore 2011 and [Influenza Antiviral Medications: Summary for Clinicians](#) for further details.

<sup>d</sup> See Acosta et al. *J Infect Dis* 2010; 202:563-566 for dosing recommendations in premature infants.

<sup>e</sup> Oseltamivir is FDA-approved for treatment of influenza in children aged ≥2 weeks; however, both CDC and AAP recommend use of oral oseltamivir for influenza treatment in infants aged <2 weeks.

<sup>f</sup> Zanamivir **is not recommended** for treatment in children aged <7 years or for children with underlying respiratory disease.

**Key:** AAP = American Academy of Pediatrics; CDC = Centers for Disease Control and Prevention; CrCl = creatinine clearance; ESRD = end stage renal disease; FDA = Food and Drug Administration; PK = pharmacokinetic

## References

1. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. *Lancet Infect Dis*. 2007;7(4):257-265. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17376383>.
2. Cox NJ, Subbarao K. Influenza. *Lancet*. 1999;354(9186):1277-1282. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10520648>.
3. Hall CB, Douglas RG, Jr. Nosocomial influenza infection as a cause of intercurrent fevers in infants. *Pediatrics*. 1975;55(5):673-677. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1168894>.
4. Giannella M, Alonso M, Garcia de Viedma D, et al. Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. *Clin Microbiol Infect*. 2011;17(8):1160-1165. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20946412>.
5. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis*. 2009;200(4):492-500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19591575>.
6. Klimov AI, Rocha E, Hayden FG, Shult PA, Roumillat LF, Cox NJ. Prolonged shedding of amantadine-resistant influenza A viruses by immunodeficient patients: detection by polymerase chain reaction-restriction analysis. *J Infect Dis*. 1995;172(5):1352-1355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7594676>.
7. Frank AL, Taber LH, Wells CR, Wells JM, Glezen WP, Paredes A. Patterns of shedding of myxoviruses and paramyxoviruses in children. *J Infect Dis*. 1981;144(5):433-441. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6273473>.
8. Bridges CB, Fry A, et al. Influenza. In: D.L. H, ed. *Control of Communicable Diseases Manual*. 19th edition. Washington, DC. 2008:315-331.
9. Calvo C, Garcia-Garcia ML, Borrell B, Pozo F, Casas I. Prospective study of influenza C in hospitalized children. *Pediatr Infect Dis J*. 2013;32(8):916-919. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23624431>.
10. Principi N, Scala A, Daleno C, Esposito S. Influenza C virus-associated community-acquired pneumonia in children. *Influenza Other Respir Viruses*. 2013;7(6):999-1003. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23594251>.
11. Shimizu Y, Abiko C, Ikeda T, Mizuta K, Matsuzaki Y. Influenza C virus and human metapneumovirus infections in hospitalized children with lower respiratory tract illness. *Pediatr Infect Dis J*. 2015;34(11):1273-1275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26244834>.
12. Pabbaraju K, Wong S, Wong A, May-Hadford J, Tellier R, Fonseca K. Detection of influenza C virus by a real-time RT-PCR assay. *Influenza Other Respir Viruses*. 2013;7(6):954-960. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23445084>.

13. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep*. 2010;59(RR-8):1-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20689501>.
14. Dolin R. Editorial commentary: Perspectives on the role of immunization against influenza in HIV-infected patients. *Clin Infect Dis*. 2011;52(1):147-149. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21148533>.
15. Neuzil KM, Coffey CS, Mitchel EF, Jr., Griffin MR. Cardiopulmonary hospitalizations during influenza season in adults and adolescents with advanced HIV infection. *J Acquir Immune Defic Syndr*. 2003;34(3):304-307. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14600576>.
16. Lin JC, Nichol KL. Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome. *Arch Intern Med*. 2001;161(3):441-446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11176770>.
17. Feiterna-Sperling C, Edelmann A, Nickel R, et al. Pandemic influenza A (H1N1) outbreak among 15 school-aged HIV-1-infected children. *Clin Infect Dis*. 2010;51(11):e90-94. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21039216>.
18. Noguera-Julian A, Provens AC, Soler-Palacin P, et al. Pandemic influenza a (2009 H1N1) in human immunodeficiency virus-infected catalan children. *Pediatr Infect Dis J*. 2011;30(2):173-175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20802374>.
19. Cohen C, Simonsen L, Sample J, et al. Influenza-related mortality among adults aged 25-54 years with AIDS in South Africa and the United States of America. *Clin Infect Dis*. 2012;55(7):996-1003. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22715173>.
20. Tempia S, Walaza S, Viboud C, et al. Mortality associated with seasonal and pandemic influenza and respiratory syncytial virus among children <5 years of age in a high HIV prevalence setting--South Africa, 1998-2009. *Clin Infect Dis*. 2014;58(9):1241-1249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24567249>.
21. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. *N Engl J Med*. 2006;355(1):31-40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16822994>.
22. Madhi SA, Ramasamy N, Bessellar TG, Saloojee H, Klugman KP. Lower respiratory tract infections associated with influenza A and B viruses in an area with a high prevalence of pediatric human immunodeficiency type 1 infection. *Pediatr Infect Dis J*. 2002;21(4):291-297. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12075759>.
23. Giannattasio A, Lo Vecchio A, Russo MT, et al. Pandemic flu: a comparative evaluation of clinical, laboratory, and radiographic findings in HIV-positive and negative children. *AIDS*. 2010;24(14):2292-2294. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20639725>.

24. Centers for Disease C, Prevention. Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus - United States, 2009. *MMWR Morb Mortal Wkly Rep*. 2009;58(30):826-829. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19661856>.
25. Siegel JD, Rhinehart E, Jackson M, Chiarello L, Health Care Infection Control Practices Advisory Committee. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control*. 2007;35(10 Suppl 2):S65-164. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18068815>.
26. Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. *JAMA*. 2000;284(13):1677-1682. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11015798>.
27. Sullivan PS, Hanson DL, Dworkin MS, et al. Effect of influenza vaccination on disease progression among HIV-infected persons. *AIDS*. 2000;14(17):2781-2785. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11125897>.
28. Zanetti AR, Amendola A, Besana S, Boschini A, Tanzi E. Safety and immunogenicity of influenza vaccination in individuals infected with HIV. *Vaccine*. 2002;20 Suppl 5:B29-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12477415>.
29. Jackson CR, Vavro CL, Valentine ME, et al. Effect of influenza immunization on immunologic and virologic characteristics of pediatric patients infected with human immunodeficiency virus. *Pediatr Infect Dis J*. 1997;16(2):200-204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9041601>.
30. Esposito S, Tagliaferri L, Daleno C, et al. Pandemic influenza A/H1N1 vaccine administered sequentially or simultaneously with seasonal influenza vaccine to HIV-infected children and adolescents. *Vaccine*. 2011;29(8):1677-1682. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21199699>.
31. Keller M, Deveikis A, Cutillar-Garcia M, et al. Pneumococcal and influenza immunization and human immunodeficiency virus load in children. *Pediatr Infect Dis J*. 2000;19(7):613-618. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10917218>.
32. Vigano A, Zuccotti GV, Pacei M, et al. Humoral and cellular response to influenza vaccine in HIV-infected children with full viroimmunologic response to antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2008;48(3):289-296. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18545155>.
33. Hakim H, Allison KJ, Van de Velde LA, et al. Immunogenicity and safety of high-dose trivalent inactivated influenza vaccine compared to standard-dose vaccine in children and young adults with cancer or HIV infection. *Vaccine*. 2016;34(27):3141-3148. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27129426>.
34. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines. *MMWR Recomm Rep*. 2016;65(5):1-54. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27560619>.

35. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):309-318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24421306>.
36. King JC, Jr., Fast PE, Zangwill KM, et al. Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children. *Pediatr Infect Dis J*. 2001;20(12):1124-1131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11740317>.
37. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(1):1-24. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21248682>.
38. Takashita E, Meijer A, Lackenby A, et al. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2013-2014. *Antiviral Res*. 2015;117:27-38. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25721488>.
39. Centers for Disease Control and Prevention. FluView: 2016-2017 Influenza Season (Week 30, ending July 29th, 2017). <http://www.cdc.gov/flu/weekly/index.htm>. Accessed August 8, 2017.
40. Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians (2016-2017). <http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>. Accessed August 8, 2017.
41. Glaxo Wellcome Inc. Relenza (zanamivir for inhalation) [Package insert]. 2011. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/021036s027lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021036s027lbl.pdf).
42. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children--diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(8):1003-1032. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19281331>.
43. Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2016-2017. *Pediatrics*. 2016;138(4). Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27600320>.
44. de Jong MD, Ison MG, Monto AS, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. *Clin Infect Dis*. 2014;59(12):e172-185. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25115871>.
45. Hernandez JE, Adiga R, Armstrong R, et al. Clinical experience in adults and children treated with intravenous peramivir for 2009 influenza A (H1N1) under an Emergency IND program in the United States. *Clin Infect Dis*. 2011;52(6):695-706. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21367722>.
46. Sugaya N, Kohno S, Ishibashi T, Wajima T, Takahashi T. Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza



- A virus infection. *Antimicrob Agents Chemother*. 2012;56(1):369-377. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22024821>.
47. Gubareva LV, Webster RG, Hayden FG. Comparison of the activities of zanamivir, oseltamivir, and RWJ-270201 against clinical isolates of influenza virus and neuraminidase inhibitor-resistant variants. *Antimicrob Agents Chemother*. 2001;45(12):3403-3408. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11709315>.
  48. Memoli MJ, Hrabal RJ, Hassantoufighi A, Eichelberger MC, Taubenberger JK. Rapid selection of oseltamivir- and peramivir-resistant pandemic H1N1 virus during therapy in 2 immunocompromised hosts. *Clin Infect Dis*. 2010;50(9):1252-1255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20345239>.
  49. Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet*. 2000;355(9218):1845-1850. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10866439>.
  50. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20(2):127-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11224828>.
  51. DailyMed (NLM/NIH). TAMIFLU (Oseltamivir Phosphate) Drug label information. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ee3c9555-60f2-4f82-a760-11983c86e97b>. Accessed August 8, 2017.
  52. Toovey S, Rayner C, Prinssen E, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug Saf*. 2008;31(12):1097-1114. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19026027>.
  53. Budnitz DS, Lewis LL, Shehab N, Birnkrant D. CDC and FDA response to risk of confusion in dosing Tamiflu oral suspension. *N Engl J Med*. 2009;361(19):1913-1914. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19797275>.
  54. Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. *Canadian Medical Association Journal*. 2010;182(4):357-363. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2831695/>.
  55. Lee N, Hui DS, Zuo Z, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza A and B infections. *Clin Infect Dis*. 2013;57(11):1511-1519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24046309>.
  56. Yu Y, Garg S, Yu PA, et al. Peramivir use for treatment of hospitalized patients with influenza A(H1N1)pdm09 under emergency use authorization, October 2009-June 2010. *Clin Infect Dis*. 2012;55(1):8-15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22491506>.
  57. Louie JK, Yang S, Samuel MC, Uyeki TM, Schechter R. Neuraminidase inhibitors for critically ill children with influenza. *Pediatrics*. 2013;132(6):e1539-1545. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24276847>.



58. Chadwick EG, Chang G, Decker MD, Yogev R, Dimichele D, Edwards KM. Serologic response to standard inactivated influenza vaccine in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 1994;13(3):206-211. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8177629>.
59. Montoya CJ, Toro MF, Aguirre C, et al. Abnormal humoral immune response to influenza vaccination in pediatric type-1 human immunodeficiency virus infected patients receiving highly active antiretroviral therapy. *Mem Inst Oswaldo Cruz*. 2007;102(4):501-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17612772>.
60. Weinberg A, Song LY, Walker R, et al. Anti-influenza serum and mucosal antibody responses after administration of live attenuated or inactivated influenza vaccines to HIV-infected children. *J Acquir Immune Defic Syndr*. 2010;55(2):189-196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20581690>.
61. Machado AA, Machado CM, Boas LS, et al. Short communication: immunogenicity of an inactivated influenza vaccine and postvaccination influenza surveillance in HIV-infected and noninfected children and adolescents. *AIDS Res Hum Retroviruses*. 2011;27(9):999-1003. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21284525>.
62. Lyall EG, Charlett A, Watkins P, Zambon M. Response to influenza virus vaccination in vertical HIV infection. *Arch Dis Child*. 1997;76(3):215-218. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9135261>.
63. Kosalaraksa P, Srirompotong U, Newman RW, Lumbiganon P, Wood JM. Serological response to trivalent inactive influenza vaccine in HIV-infected children with different immunologic status. *Vaccine*. 2011;29(16):3055-3060. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21349365>.
64. Hakim H, Allison KJ, Van De Velde LA, Li Y, Flynn PM, McCullers JA. Immunogenicity and safety of inactivated monovalent 2009 H1N1 influenza A vaccine in immunocompromised children and young adults. *Vaccine*. 2012;30(5):879-885. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22155630>.
65. Flynn PM, Nachman S, Muresan P, et al. Safety and immunogenicity of 2009 pandemic H1N1 influenza vaccination in perinatally HIV-1-infected children, adolescents, and young adults. *J Infect Dis*. 2012;206(3):421-430. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22615311>.
66. Madhi SA, Dittmer S, Kuwanda L, et al. Efficacy and immunogenicity of influenza vaccine in HIV-infected children: a randomized, double-blind, placebo controlled trial. *AIDS*. 2013;27(3):369-379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23032417>.
67. Madhi SA, Maskew M, Koen A, et al. Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety. *Clin Infect Dis*. 2011;52(1):128-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21148531>.
68. King JC, Jr., Treanor J, Fast PE, et al. Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted,

- administered to human immunodeficiency virus (HIV)-infected and non-HIV-infected adults. *J Infect Dis.* 2000;181(2):725-728. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10669363>.
69. Levin MJ, Song LY, Fenton T, et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. *Vaccine.* 2008;26(33):4210-4217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18597900>.
  70. Pass RF, Nachman S, Flynn PM, et al. Immunogenicity of licensed influenza A (H1N1) 2009 monovalent vaccines in HIV-infected children and youth. *J Pediatric Infect Dis Soc.* 2013;2(4):352-360. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24363932>.
  71. Grohskopf LA, Olsen SJ, Sokolow LZ, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) -- United States, 2014-15 influenza season. *MMWR Morb Mortal Wkly Rep.* 2014;63(32):691-697. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25121712>.
  72. Roussy JF, Abed Y, Bouhy X, Boivin G. Emergence of an oseltamivir-resistant influenza A/H3N2 virus in an elderly patient receiving a suboptimal dose of antiviral prophylaxis. *J Clin Microbiol.* 2013;51(12):4234-4236. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24088848>.
  73. Baz M, Abed Y, Boivin G. Characterization of drug-resistant recombinant influenza A/H1N1 viruses selected in vitro with peramivir and zanamivir. *Antiviral Res.* 2007;74(2):159-162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17137644>.
  74. Hurt AC, Chotpitayasunondh T, Cox NJ, et al. Antiviral resistance during the 2009 influenza A H1N1 pandemic: public health, laboratory, and clinical perspectives. *Lancet Infect Dis.* 2012;12(3):240-248. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22186145>.
  75. Pizzorno A, Abed Y, Plante PL, et al. Evolution of oseltamivir resistance mutations in Influenza A(H1N1) and A(H3N2) viruses during selection in experimentally infected mice. *Antimicrob Agents Chemother.* 2014;58(11):6398-6405. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25114143>.

# Progressive Multifocal Leukoencephalopathy

Updated: October 6, 2013

Reviewed: October 6, 2013

Panel's Recommendations
<ul style="list-style-type: none"><li>• The main approach to treatment of Progressive Multifocal Leukoencephalopathy (PML) is treatment with an effective antiretroviral regimen that suppresses HIV viremia and preserves or restores CD4 T lymphocyte (CD4) cell-defined immune function <b>(AII)</b>.</li><li>• Intrathecal cytosine arabinoside and cidofovir are not routinely recommended for treatment of PML <b>(BIII)</b>.</li><li>• Immunomodulatory approaches, such as interferon alfa, are not routinely recommended for treatment of PML <b>(BIII)</b>.</li></ul>
<p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional</p> <p><b>Rating of Evidence:</b> I = One or more randomized trials <b>in children</b><sup>†</sup> with clinical outcomes and/or validated endpoints; I* = One or more randomized trials <b>in adults</b> with clinical outcomes and/or validated laboratory endpoints with accompanying data <b>in children</b><sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies <b>in children</b><sup>†</sup> with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies <b>in adults</b> with long-term clinical outcomes with accompanying data <b>in children</b><sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion</p> <p><sup>†</sup>Studies that include children or children/adolescents, but not studies limited to post pubertal adolescents</p>

## Epidemiology

First described in association with disorders of B-cell function, such as chronic lymphocytic leukemia and Hodgkin disease, progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system (CNS) that occurs in immunocompromised patients.<sup>1</sup> In HIV-infected adults, CD4 T lymphocyte (CD4 cell) counts less than 100 cells/mm<sup>3</sup> are associated with development of PML, and persistence of CD4 counts less than 50 to 100 cells/mm<sup>3</sup> are associated with fatal PML. Not all patients with PML have severe immune dysfunction, however, and PML has been reported in HIV-infected patients with high CD4 counts who are receiving successful combination antiretroviral therapy (cART).

PML is caused by JC virus (JCV), a ubiquitous polyomavirus, named using the initials of the patient, John Cunningham, from whom it was first isolated. Most humans are infected with JCV early in life; in a seroepidemiology study, 50% of Swedish children were seropositive for JCV by ages 9 to 11 years, and 72% of adult women aged ≥25 years in the Finnish Maternity Cohort were JCV seropositive.<sup>2</sup> The exact mode of transmission of JCV between individuals is unknown. Because the virus is commonly detected in urine, JCV has been detected in sewage effluent. It is also detectable in peripheral blood mononuclear cells of both healthy and immunocompromised individuals. Vertical transmission from mother to newborn also has been documented.<sup>3,4</sup> Lymphocytes, renal tubular epithelium, bone marrow, and possibly spleen and lymphoid tissue likely represent sites of viral latency, and lymphocytes also may be a vehicle for spread of the virus to other organ systems, including the CNS.<sup>5,6</sup>

The evolution of asymptomatic infection with JCV to symptomatic PML probably involves a series of events that are both virologic and immunologic. The original infecting strain of JCV—the strain

that is commonly detected in urine and blood—mutates and alters a regulatory gene through rearrangement of a non-coding region (at-NCCR to rr-NCCR) to become a neurotropic strain of JCV capable of replicating in neuronal glial cells.<sup>7</sup> Failed immune surveillance allows replicating virus to persist in peripheral blood cells and serum. If the neurotropic form of JCV gains entry into the brain, it can then establish a productive infection in oligodendrocyte cells, which leads to PML in the absence of proper CNS immune surveillance.<sup>8</sup> Serotonin receptor 5-HT(2a) appears important for JCV infection of brain glial cells.<sup>9</sup> Recently, in HIV-uninfected adults, an increased incidence of PML has been associated with use of therapeutic monoclonal antibodies, including natalizumab (an alpha 4 beta 1 and alpha 4 beta 7 antagonist that targets activated lymphocytes), efalizumab (an anti CD-11a antibody that targets T-lymphocytes), rituximab (an anti CD-20 antibody that targets B-lymphocytes), and alemtuzumab (an anti-CD52 antibody that depletes both T and B cells).<sup>8, 10-12</sup>

PML is an AIDS-defining illness in HIV-infected individuals. It has rarely been seen in reports from large series of HIV-infected children,<sup>13-15</sup> but cases have been reported in children with a wide range of ages and a broad geographical distribution.<sup>16-22</sup> The incidence of PML has decreased from 3.3 cases per 1000 person-years at risk during the era before cART, to 1.3 cases per 1000 person-years after the introduction of cART.<sup>23</sup> During the pre-cART era, survival was extremely poor in adults and children with PML.<sup>15</sup> Survival among adults has improved during the cART era<sup>24-26</sup> from 10% to 50%, and mean survival time from time of diagnosis of PML has increased from 0.4 years to 1.8 years.<sup>27</sup> No comparable data exist for children.

## Clinical Manifestations

No symptoms are known to be associated with acute or latent JCV infection. Asymptomatic urinary shedding is common. PML is the primary disease caused by JCV and clinical manifestations in children are similar to those in adults. The disease has an insidious onset and produces a neurologic syndrome that steadily progresses over weeks or months, characterized by confusion, disorientation, lack of energy, loss of balance, cognitive dysfunction, dementia, seizures, ataxia, aphasia, cranial nerve deficits, visual abnormalities (blurred or double vision or loss of vision), hemiparesis or quadriparesis, and eventually coma.

Demyelination is at first patchy, involving subcortical regions, and then spreads to deep white matter in a confluent pattern; thus, PML initially may present with focal neurologic deficits that involve different brain regions.

## Diagnosis

The established criteria for clinical diagnosis are focal signs and symptoms on neurologic examination, focal white matter lesions on magnetic resonance imaging (MRI) or computerized tomography (CT) without mass effect, and exclusion of other causes of the clinical and neuroradiologic findings.<sup>28</sup> A confirmed diagnosis of PML requires a compatible clinical syndrome and radiographic findings, coupled with brain biopsy demonstrating a characteristic triad of pathologic foci of demyelination, enlarged hyperchromatic oligodendrocytes with enlarged nuclei and basophilic-staining intranuclear material, and enlarged astrocytes with bizarre hyperchromatic nuclei. When only two of these features are present, JCV can be demonstrated by *in situ* hybridization or by electron microscopy for definitive diagnosis.

Brain biopsy remains the gold standard confirmatory test for diagnosis of PML, but brain imaging with MRI or CT can reveal characteristic lesions. The radiologic features of PML are typically non-

inflammatory (unless associated with immune reconstitution inflammatory syndrome [IRIS] related to initiation of cART). Typical CT abnormalities include single or multiple hypodense, non-enhancing cerebral white matter lesions; cerebellum and brain stem occasionally are involved. MRI may be more sensitive for detecting changes in the brain associated with PML, and may be positive before JCV DNA is detected in the cerebrospinal fluid (CSF). MRI depicts white matter lesions of low T1 signal intensity and high proton density on T2-weighted images with absence of edema or mass effect. Post-contrast enhancement is unusual, and when present, usually is sparse, with a thin or reticulated appearance adjacent to the edge of the lesions.

PML diagnosis is now facilitated by use of a polymerase chain reaction (PCR) assay to detect JCV DNA in CSF, which may obviate the need for brain biopsy in patients with a compatible clinical syndrome and radiographic findings. Nested JCV DNA PCR on CSF is highly sensitive (90%–100%) and specific (92%–100%) for PML in adults, and in the absence of comparative data for children, similar performance characteristics are anticipated but not proven in that population.<sup>29</sup> False-negative tests occur, however, and PML may be present and diagnosed by brain biopsy in patients with a negative JCV DNA PCR test in the CSF. Measurement of JCV DNA levels in CSF samples can be a useful virologic marker for managing PML in patients receiving cART.<sup>30</sup> With the advent of multiple modalities to support PML diagnosis, diagnostic criteria can be stratified according to the following terminology and levels of certainty of diagnosis:

- **Biopsy-confirmed PML:** JCV antigens detected by immunohistochemistry, JCV DNA detected by *in situ* nucleic acid hybridization, or JC virions detected by electron microscopy in brain tissue obtained by cerebral biopsy, associated with typical histology, in patients with typical clinical and radiological findings
- **Laboratory-confirmed PML:** JCV DNA detected by PCR of CSF in patients with typical, clinical, and radiological findings (detection of intrathecal antibody production may also support the diagnosis)
- **Possible PML:** Patients with typical clinical and radiological findings, without virologic or histologic confirmation in brain tissue or CSF.<sup>31, 32</sup>

Presence of antibodies to JCV in the serum or presence of JCV DNA in the blood or urine of patients does not establish the diagnosis of PML because these studies can be positive in individuals without PML. Conversely, while most patients with JCV-associated PML have moderate to high anti-JCV antibodies and JCV DNA in their peripheral blood, serum, and CSF, some patients with PML diagnosed by brain biopsy will not have detectable anti-JCV antibody or JCV DNA in their blood or CSF. Most patients with JCV-associated PML, however, have moderate to high anti-JCV antibodies and JCV DNA in their peripheral blood, serum, and CSF.

## Prevention Recommendations

### *Preventing Exposure*

There is no known way to prevent exposure to JCV.

## ***Preventing First Episode of Disease***

Use of cART can prevent or reverse the severe immunosuppression that increases the risk of PML. Incidence of PML has decreased in the cART era. There are no means of preventing PML in severely immunosuppressed individuals.

## ***Discontinuing Primary Prophylaxis***

No means of primary prophylaxis of JCV infection or development of PML have been demonstrated.

## **Treatment Recommendations**

### ***Treating Disease***

No effective specific therapy has been established for JCV infection or PML. Survival in HIV-infected adults with PML has substantially improved during the post-cART era, with an increase in median survival from 14 to 64 weeks.<sup>27, 33</sup> A CD4 count >100 cells/mm<sup>3</sup> at PML diagnosis is associated with improved survival, and use of cART after diagnosis of PML is strongly associated with improved survival.<sup>33</sup> Thus, the main approach to treatment involves optimizing cART to reverse the immunosuppression that interferes with normal host response to this virus (**AII**).

A number of agents have been proposed or reported anecdotally as more specific treatments for PML, but none has proven effective after greater scrutiny or more extensive study. In a randomized, open-label trial of intravenous (IV) and intrathecal cytosine arabinoside<sup>34</sup> and a non-randomized, open-label trial of IV cidofovir,<sup>35</sup> neither drug was effective in producing clinical improvement of PML in HIV-infected adults, and neither agent is routinely recommended (**BIII**). Immunomodulatory approaches such as interferon-alfa (IFN- $\alpha$ ) also have been described in case reports in HIV-infected adults; however, none have been studied in a controlled clinical trial and, in one analysis, these approaches did not provide any benefit beyond that with cART.<sup>36</sup> Thus, they are also not routinely recommended (**BIII**). Anecdotal reports have been published about use of mirtazapine (a 5-HT(2a) receptor antagonist) plus either cidofovir or cytosine-arabinside, with tapering of immunosuppressive therapy, to treat PML in HIV-uninfected adults who developed the disease while on immunosuppressive therapy. While the results with this adjunctive treatment are encouraging, there is insufficient evidence to recommend it at this time.<sup>31, 37, 38</sup> In addition, recent *in vitro* studies have shown that CMX001, an investigational oral ester form of cidofovir, suppresses JCV replication in human brain cell cultures, and the compound may be evaluated in clinical trials in the near future.<sup>39, 40</sup> No therapeutic trials have been conducted in children.

### ***Monitoring and Adverse Events, Including IRIS***

Patients may develop PML before starting cART or may manifest PML as an unmasking IRIS event after immune reconstitution with antiretroviral therapy (ART). Neurologic stability or improvement and prolonged survival are associated with reduced levels of JCV DNA in CSF, appearance of JCV-specific antibody in CSF, and presence of JCV-specific cytotoxic T-cell responses in patients receiving cART.<sup>41</sup>

After cART is initiated and CD4 counts rise, some patients will experience neurologic improvement; however, reports have documented worsening neurologic manifestations after initiation of ART.<sup>26</sup> Clinical worsening may represent the natural history of PML in these patients. However, this



apparent worsening may also be a paradoxical reaction from inflammatory responses to JCV potentiated by cART-induced immune reconstitution, called IRIS,<sup>26, 42-44</sup> examples of which have occurred in children.<sup>45</sup> The underlying mechanism of cART-associated PML IRIS is controversial. One hypothesis is that a reduction in inhibitory cytokines (e.g., IFN- $\alpha$  and interleukin-12) after cART promotes JCV re-activation within the brain or increases trafficking of JCV-infected peripheral lymphocytes into the brain.<sup>46</sup> Another possibility is that JCV infection occurring coincidental to cART initiation results in a beneficial inflammatory response, with lack of disease progression.<sup>46</sup> This may be particularly likely in cases of perinatal HIV infection, because JCV acquisition is most common early in life. The overall prevalence of PML-associated IRIS in children is unknown. Inflammatory PML should be suspected in cART-treated children with advanced HIV who show acute neurologic deterioration and contrast-enhancing demyelinating lesions on MRI, even if immunological and virological measures show improvement in HIV status.<sup>22</sup> Retrospective data suggest that early and prolonged treatment with steroids may be beneficial for some patients in whom immune reconstitution with ART activates an inflammatory response to JCV. No clinical trial data exist, however, to substantiate the anecdotal evidence.<sup>47</sup>

### ***Managing Treatment Failure***

PML remission with cART may take several weeks, and no criteria exist that define progression of disease. A working definition of treatment failure used for HIV-infected adults is continued clinical worsening and continued detection of CSF JCV DNA at 3 months (see [\*Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults\*](#)).<sup>48</sup> In addition, lack of JCV antibody response or JCV-specific cytotoxic T-cell immune responses are associated with poor prognosis. In some patients, PML worsens despite cART, either because of IRIS or because of the natural history of PML. Whichever is the case, cART should be continued. If cART fails to suppress HIV RNA or to increase the CD4 count, then attention should focus on modifying and optimizing the cART (**AII**). In HIV-infected children responding well to cART but with continued worsening of PML, an expert in pediatric HIV infection should be consulted for consideration of investigational therapies.

### ***Preventing Recurrence***

On the basis of its role in reversing the disease, the main measure for preventing PML recurrence is an effective cART regimen that suppresses HIV viremia and preserves or restores CD4-defined immune function (**AII**).

### ***Discontinuing Secondary Prophylaxis***

No methods for secondary prophylaxis of JCV infection or PML have been proven effective.

## References

1. Astrom KE, Mancall EL, Richardson EP, Jr. Progressive multifocal leuco-encephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. *Brain*. 1958;81(1):93-111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/13523006>.
2. Stolt A, Sasnauskas K, Koskela P, Lehtinen M, Dillner J. Seroepidemiology of the human polyomaviruses. *J Gen Virol*. 2003;84(Pt 6):1499-1504. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12771419>.
3. White MK, Khalili K. Pathogenesis of progressive multifocal leukoencephalopathy--revisited. *J Infect Dis*. 2011;203(5):578-586. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21227915>.
4. Boldorini R, Allegrini S, Miglio U, et al. Serological evidence of vertical transmission of JC and BK polyomaviruses in humans. *J Gen Virol*. 2011;92(Pt 5):1044-1050. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21307224>.
5. Rodrigues C, Pinto D, Medeiros R. Molecular epidemiology characterization of the urinary excretion of polyomavirus in healthy individuals from Portugal--a Southern European population. *J Med Virol*. 2007;79(8):1194-1198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17596822>.
6. Gu ZY, Li Q, Si YL, Li X, Hao HJ, Song HJ. Prevalence of BK virus and JC virus in peripheral blood leukocytes and normal arterial walls in healthy individuals in China. *J Med Virol*. 2003;70(4):600-605. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12794723>.
7. Gosert R, Kardas P, Major EO, Hirsch HH. Rearranged JC virus noncoding control regions found in progressive multifocal leukoencephalopathy patient samples increase virus early gene expression and replication rate. *J Virol*. 2010;84(20):10448-10456. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20686041>.
8. Berger JR, Houff SA, Major EO. Monoclonal antibodies and progressive multifocal leukoencephalopathy. *MAbs*. 2009;1(6):583-589. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20073129>.
9. Focosi D, Kast RE, Maggi F, Ceccherini-Nelli L, Petrini M. Sialic acid moieties and 5-HT2a: two faces of the same receptor for JC virus? *J Clin Virol*. 2008;43(1):132-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18534904>.
10. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. *Lancet Oncol*. 2009;10(8):816-824. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19647202>.
11. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. *Annu Rev Med*. 2010;61:35-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19719397>.



12. Gea-Banacloche JC. Rituximab-associated infections. *Semin Hematol*. 2010;47(2):187-198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20350666>.
13. Dankner WM, Lindsey JC, Levin MJ, Pediatric ACTGPT. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. *Pediatr Infect Dis J*. 2001;20(1):40-48. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11176565>.
14. Nesheim SR, Kapogiannis BG, Soe MM, et al. Trends in opportunistic infections in the pre- and post-highly active antiretroviral therapy eras among HIV-infected children in the perinatal AIDS collaborative transmission study, 1986-2004. *Pediatrics*. 2007;120(1):100-109. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17606567>.
15. Ciuta ST, Boros S, Napoli PA, Pezzotti P, Rezza G. Predictors of survival in children with acquired immunodeficiency syndrome in Italy, 1983 to 1995. *AIDS Patient Care STDS*. 1998;12(8):629-637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15468435>.
16. Araujo AP, Pereira HS, Oliveira RH, Frota AC, Esperanca JC, Duarte F. Progressive multifocal leukoencephalopathy in a child with acquired immunodeficiency syndrome (AIDS). *Arq Neuropsiquiatr*. 1997;55(1):122-125. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9332571>.
17. Robinson LG, Chiriboga CA, Champion SE, Ainyette I, DiGrado M, Abrams EJ. Progressive multifocal leukoencephalopathy successfully treated with highly active antiretroviral therapy and cidofovir in an adolescent infected with perinatal human immunodeficiency virus (HIV). *J Child Neurol*. 2004;19(1):35-38. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15032381>.
18. Wilmshurst JM, Burgess J, Hartley P, Eley B. Specific neurologic complications of human immunodeficiency virus type 1 (HIV-1) infection in children. *J Child Neurol*. 2006;21(9):788-794. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16970887>.
19. Shah I, Chudgar P. Progressive multifocal leukoencephalopathy (PML) presenting as intractable dystonia in an HIV-infected child. *J Trop Pediatr*. 2005;51(6):380-382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15927949>.
20. Berger JR, Scott G, Albrecht J, Belman AL, Tornatore C, Major EO. Progressive multifocal leukoencephalopathy in HIV-1-infected children. *AIDS*. 1992;6(8):837-841. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1418781>.
21. Liptai Z, Papp E, Barsi P, et al. Progressive multifocal leukoencephalopathy in an HIV-infected child. *Neuropediatrics*. 2007;38(1):32-35. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17607602>.
22. Oberdorfer P, Washington CH, Katanyuwong K, Jittamala P. Progressive multifocal leukoencephalopathy in HIV-infected children: a case report and literature review. *Int J Pediatr*. 2009;2009:348507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20041004>.
23. Engsig FN, Hansen AB, Omland LH, et al. Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIV-infected patients during the highly active

- antiretroviral therapy era: a nationwide cohort study. *J Infect Dis*. 2009;199(1):77-83. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19007313>.
24. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol*. 2003;9 Suppl 1:47-53. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12709872>.
  25. Koralnik IJ. New insights into progressive multifocal leukoencephalopathy. *Curr Opin Neurol*. 2004;17(3):365-370. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15167073>.
  26. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis*. 2003;36(8):1047-1052. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12684918>.
  27. Lima MA, Bernal-Cano F, Clifford DB, Gandhi RT, Koralnik IJ. Clinical outcome of long-term survivors of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*. 2010;81(11):1288-1291. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20710013>.
  28. Angelini L, Pietrogrande MC, Delle Piane MR, et al. Progressive multifocal leukoencephalopathy in a child with hyperimmunoglobulin E recurrent infection syndrome and review of the literature. *Neuropediatrics*. 2001;32(5):250-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11748496>.
  29. Mamidi A, DeSimone JA, Pomerantz RJ. Central nervous system infections in individuals with HIV-1 infection. *J Neurovirol*. 2002;8(3):158-167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12053271>.
  30. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis*. 2005;40(5):738-744. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15714422>.
  31. Focosi D, Marco T, Kast RE, Maggi F, Ceccherini-Nelli L, Petrini M. Progressive multifocal leukoencephalopathy: what's new? *Neuroscientist*. 2010;16(3):308-323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20479473>.
  32. Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis*. 2009;9(10):625-636. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19778765>.
  33. Drake AK, Loy CT, Brew BJ, et al. Human immunodeficiency virus-associated progressive multifocal leukoencephalopathy: epidemiology and predictive factors for prolonged survival. *Eur J Neurol*. 2007;14(4):418-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17388991>.
  34. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. *AIDS*

- Clinical Trials Group 243 Team. *N Engl J Med*. 1998;338(19):1345-1351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9571254>.
35. Marra CM, Rajcic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS*. 2002;16(13):1791-1797. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12218391>.
  36. Geschwind MD, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol*. 2001;7(4):353-357. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11517416>.
  37. Vulliemoz S, F. Lurati-Ruiz, et al. Favourable outcome of progressive multifocal leukoencephalopathy in two patients with dermatomyositis. *J Neurol Neurosurg Psychiatry*. 77(9): 1079-82. 2006. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16914758>.
  38. Owczarczyk K, Hilker R, Brunn A, Hallek M, Rubbert A. Progressive multifocal leukoencephalopathy in a patient with sarcoidosis--successful treatment with cidofovir and mirtazapine. *Rheumatology (Oxford)*. 2007;46(5):888-890. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17389659>.
  39. Jiang ZG, Cohen J, Marshall LJ, Major EO. Hexadecyloxypropyl-cidofovir (CMX001) suppresses JC virus replication in human fetal brain SVG cell cultures. *Antimicrob Agents Chemother*. 2010;54(11):4723-4732. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20823288>.
  40. Gosert R, Rinaldo CH, Wernli M, Major EO, Hirsch HH. CMX001 (1-O-hexadecyloxypropyl-cidofovir) inhibits polyomavirus JC replication in human brain progenitor-derived astrocytes. *Antimicrob Agents Chemother*. 2011;55(5):2129-2136. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21402853>.
  41. Giudici B, Vaz B, Bossolasco S, et al. Highly active antiretroviral therapy and progressive multifocal leukoencephalopathy: effects on cerebrospinal fluid markers of JC virus replication and immune response. *Clin Infect Dis*. 2000;30(1):95-99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10619739>.
  42. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis*. 2002;35(10):1250-1257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12410486>.
  43. Cinque P, Koralnik IJ, Clifford DB. The evolving face of human immunodeficiency virus-related progressive multifocal leukoencephalopathy: defining a consensus terminology. *J Neurovirol*. 2003;9 Suppl 1:88-92. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12709878>.
  44. D'Amico R, Sarkar S, Yusuff J, Azar E, Perlman DC. Immune reconstitution after potent antiretroviral therapy in AIDS patients with progressive multifocal leukoencephalopathy.

- Scand J Infect Dis.* 2007;39(4):347-350. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/17454900>.
45. Nuttall JJ, Wilmshurst JM, Ndondo AP, et al. Progressive multifocal leukoencephalopathy after initiation of highly active antiretroviral therapy in a child with advanced human immunodeficiency virus infection: a case of immune reconstitution inflammatory syndrome. *Pediatr Infect Dis J.* 2004;23(7):683-685. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/15247614>.
  46. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol.* 2003;9 Suppl 1(Suppl 1):25-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12709868>.
  47. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology.* 2009;72(17):1458-1464. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19129505>.
  48. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the national institutes of health, and the HIV medicine association of the infectious diseases society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207; quiz CE201-204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19357635>.