Opportunistic Infections

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Objectives

1. Define opportunistic infections (OIs) in people with human immunodeficiency virus (HIV)/AIDS.
2. Describe primary prophylaxis to prevent OIs in people with HIV/AIDS.
3. Evaluate the clinical manifestations of bacterial, viral, parasitic, and fungal OIs in people with HIV/AIDS.
4. Describe the treatment for bacterial, viral, parasitic, and fungal OIs in people with HIV/AIDS.
5. Review specific interventions that can decrease the development of OIs in people with HIV/AIDS.

Key Points

1. An OI is caused by organisms that would not produce significant disease in a person with a well-functioning immune system.
2. People with HIV/AIDS are susceptible to OIs because their immune systems have been suppressed and cannot fight disease.
3. People with HIV/AIDS may have OIs at diagnosis.
4. Primary prophylaxis, or preventive treatment, is used to prevent OIs in people with HIV/AIDS.
5. Viral infections found in people with HIV/AIDS include cytomegalovirus, varicella-zoster (shingles), herpes simplex, hepatitis, and Epstein-Barr virus.
6. *Pneumocystis jirovecii* can cause severe pneumonia in people with HIV/AIDS.
7. Prophylaxis for *Pneumocystis jirovecii* is recommended for people with HIV/AIDS.
8. *Candida albicans* is the most common fungal infection diagnosed in HIV-infected people.
9. Education regarding appropriate preparation of food and good hygiene principles is essential to prevent serious OIs.

Overview

Many people living with human immunodeficiency virus (HIV)/AIDS acquire diseases that also affect otherwise healthy people. In such cases, HIV-infected patients may have a more severe disease course than uninfected people or may develop symptoms that uninfected people do not. However, HIV-infected people are also susceptible to opportunistic infections (OIs), which are infections caused by organisms that in a healthy host would not cause significant disease. This module discusses both types of infection. The most common OIs vary with geographic location. This module will give a broad overview of the concepts of preventing OIs and will discuss the most commonly diagnosed diseases worldwide. The module will cover specific diseases, how to recognize them, and which medicines are recommended to treat them. Treatment recommendations are based on available information and research. Not every recommendation will be feasible in every setting. Each country and health department will need to decide which treatments are appropriate in a particular area.

People with HIV/AIDS are susceptible to OIs because of how HIV/AIDS suppresses the immune system. Many people do not know that they have HIV until the first time that they have an OI. When counseling patients with HIV, one must emphasize how to avoid OIs. Easy ways to avoid some of these infections are through general good hygiene, including thorough washing of food and hands.

People with HIV need to be especially careful about how they prepare food. Meats and poultry should be cooked thoroughly. Fruits and vegetables should be washed well. Water should be taken from the cleanest source available. If clean water is not available, water should be boiled before drinking. Infections can also be passed from person to person and through contact with fecal material. Immunocompromised people should avoid contact with ill persons and with human and animal feces.
These measures can help prevent a person from getting a serious infection.

Vaccines can also reduce an HIV-infected patient’s risk of certain infections. See the chapter on immunizations for HIV-infected children for more details.

**Primary and Secondary Prophylaxis**

Oftentimes people known to be HIV infected are given medicines to prevent developing an OI. This approach is known as primary prophylaxis. The appropriate time to begin prophylaxis depends on the age of the patient, which infection is being prevented, and what laboratory support and medications are available in a particular area. The patient’s CD4+ lymphocyte count helps to determine when to begin primary prophylaxis. For example, when CD4+ lymphocyte counts are less than 200 cells/µL or total lymphocyte counts are less than 1,200 cells/µL, adults begin taking trimethoprim-sulfamethoxazole (TMP-SMX) to prevent *Pneumocystis jirovecii* pneumonia (formerly PCP [*Pneumocystis carinii* pneumonia]) as well as other diseases, such as toxoplasmosis, malaria, and diarrheal diseases.

When a person with AIDS dies, the cause of death is most often an OI. Primary prophylaxis is a way to help patients lead longer, healthier lives. After HIV-infected patients have been treated for an OI, they should stay on a lower dose of the medicine for the rest of their lives to prevent a relapse. This approach is known as secondary prophylaxis. Many medicines used for prophylaxis have side effects. If a patient will be taking prophylactic medications for a long time, the health professional must assess for side effects each time that the patient is examined. This requirement applies regardless of whether a patient is receiving primary or secondary prophylaxis. In places where highly active antiretroviral therapy (HAART) is available, one can sometimes discontinue prophylaxis. Although these recommendations are discussed as each organism is discussed, Table 1 provides a summary.

### Table 1. Criteria for discontinuing and restarting opportunistic infection prophylaxis for HIV-infected persons

<table>
<thead>
<tr>
<th>Opportunistic Illness</th>
<th>Criteria for Discontinuing Primary Prophylaxis</th>
<th>Criteria for Restarting Primary Prophylaxis</th>
<th>Criteria for Discontinuing Secondary Prophylaxis</th>
<th>Criteria for Restarting Secondary Prophylaxis</th>
</tr>
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<tr>
<td><em>Pneumocystis</em> Pneumonia (PCP)</td>
<td>Do not discontinue in children aged &lt;1 year After ≥6 months of HAART and: Age 1 to 5 years, CD4 percentage or count is ≥15% or ≥500 cells/mm$^3$ for &gt;3 consecutive months Age ≥6 years, CD4 percentage or count is ≥15% or ≥200 cells/mm$^3$ for &gt;3 consecutive months</td>
<td>Age 1 to 5 years with CD4 percentage &lt;15% or count &lt;500 cells/mm$^3$ Age ≥6 years with CD4 percentage &lt;15% or count &lt;200 cells/mm$^3$ for &gt;3 consecutive months</td>
<td>If fulfill all of the following criteria: Completed ≥6 months of HAART Age 1 to 5 years, CD4 percentage or count is ≥15% or &gt;500 cells/mm$^3$ for &gt;3 consecutive months Age ≥6 years, CD4 percentage or count is &gt;15% or ≥200 cells/mm$^3$ for &gt;3 consecutive months</td>
<td>Age 1 to 5 years with CD4 percentage &lt;15% or count &lt;500 cells/mm$^3$ or recurrence PCP Age ≥6 years with CD4 percentage &lt;15% or CD4 count &lt;200 cells/mm$^3$ or recurrence PCP</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em> Encephalitis (TE)</td>
<td>Do not discontinue in children aged &lt;1 year Age 1 to 5 years, CD4 percentage or count is ≥15% for &gt;3 consecutive months Age ≥6 years, CD4 percentage or count is ≥15% or ≥100-200 cells/mm$^3$ for &gt;3 consecutive months</td>
<td>Age 1 to 5 years with CD4 percentage &lt;15% (CIII) Age ≥6 years with CD4 percentage &lt;15% or CD4 count &lt;100-200 cells/mm$^3$</td>
<td>If fulfill all of the following criteria: Completed ≥6 months of HAART Complete initial therapy for TE Asymptomatic for TE Age 1 to 5 years, CD4 percentage is ≥15% for &gt;3 consecutive months Age ≥6 years, CD4 percentage or count is ≥15% or ≥200 cells/mm$^3$ for &gt;3 consecutive months</td>
<td>Age 1 to 5 years with CD4 percentage &lt;15% Age ≥6 years with CD4 percentage &lt;15% or CD4 count &lt;200 cells/mm$^3$</td>
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| *Mycobacterium avium* complex (MAC) disease | • Do not discontinue in children aged <2 years  
• If age >2 years, after ≥6 months of HAART and:  
  • Age 2 to 5 years with CD4 count >200 cells/mm³ for >3 consecutive months  
  • Age ≥6 years with CD4 count >100 cells/mm³ for >3 consecutive months | • Age 2 to 5 years with CD4 count <200 cells/mm³  
• Age ≥6 years with CD4 count <100 cells/mm³ | If fulfill all of the following criteria:  
• Completed ≥6 months of HAART  
• Consultation with ophthalmologist  
• Asymptomatic for TE  
• Age 1 to 6 years with CD4 percentage ≥15% or CD4 count >500 cells/mm³ for >3 consecutive months  
• Age >6 years with CD4 count >100 cells/mm³ for >3 consecutive months  
  Routine (every 3 to 6 months) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis | • Age 2 to 5 years with CD4 count <200 cells/mm³  
• Age ≥6 years with CD4 count <100 cells/mm³ |
| Cytomegalovirus retinitis | • Not Applicable | • Not applicable | If fulfill all of the following criteria:  
• Asymptomatic on ≥6 months of secondary prophylaxis for cryptococcosis  
• Completed ≥6 months of HAART  
• Age >6 years with CD4 count ≥200 cells/mm³ for >6 consecutive months | CD4 count <200 cells/mm³ |
| Cryptococcal meningitis | • Not Applicable | • Not applicable | If fulfill all of the following criteria:  
• CD4 count ≥150 cells/mm³ or percentage ≥15%  
• Negative *Histoplasma* blood cultures  
• Serum *Histoplasma* antigen <2 ng/mL | CD4 count <150 cells/mm³ or percentage <15% |
| *Histoplasma capsulatum* infection | | | | |
Bacterial Infections

Streptococcus pneumoniae
One of the most common serious bacterial infections is *Streptococcus pneumoniae*, which causes pneumonia, otitis media, septicemia, and other invasive illnesses. All patients with HIV who are older than 2 years should be given the 23-valent polysaccharide vaccine for pneumococcus with one revaccination 3-5 years later if the child is younger than 10 years or after 5 years if the child is older than 10 years. The heptavalent pneumococcal conjugate vaccine (PCV-7) for pneumococcus is recommended for all children as young as 2 months where available.

Treponema pallidum
*Treponema pallidum* is the anaerobic bacterium responsible for syphilis. Syphilis is not an OI in a strict sense, but coinfection with HIV and syphilis is common. In the United States, the median HIV seroprevalence among persons infected with syphilis was 15.7%. There also are indications that HIV type 1 alters the diagnosis, natural history, management, and outcome of syphilis infections. *Treponema pallidum* can be transmitted from mother to child at any stage of pregnancy or delivery.

Primary syphilis ordinarily presents as one painless nodule at the site of inoculation or contact that ulcerates into a chancre. Such ulcerations might facilitate transmission of HIV infection between partners. In an HIV-infected person, multiple or atypical chancres can occur, and primary lesions may be absent or missed. Asymptomatic primary syphilis occurs at a higher rate in HIV-infected patients.

Secondary syphilis occurs 2-8 weeks after primary inoculation. Manifestations involve all organ systems. Skin lesions (macular, maculopapular, pustular, or condyloma lata in moist or intertrigonal areas) usually begin on the trunk and spread peripherally. Characteristically they are found on the palms and soles and are accompanied by generalized lymphadenopathy and constitutional symptoms (fever, malaise, anorexia, arthralgias, headache). Secondary syphilis can be difficult to distinguish from primary HIV infection. HIV infection can cause more rapid progression of syphilis.

Late syphilis includes neurosyphilis, cardiovascular syphilis, and gummatous syphilis. Neurosyphilis can have a more rapid progression in HIV-infected patients. Although in general neurosyphilis manifests similarly in HIV-infected and uninfected individuals, concomitant uveitis and meningitis may be more common in HIV-infected persons with syphilis.

Congenital syphilis has been found in 60%-100% of infants born to mothers who are untreated or inadequately treated for primary or secondary syphilis. Infants born to HIV-infected women have a higher rate of congenital syphilis than that of the general population. Coinfection may also increase the rate of perinatal HIV transmission. Clinical manifestations may be asymptomatic. Other manifestations are classified as either early or late. Early manifestations include hepatosplenomegaly, jaundice, mucocutaneous lesions, skin rash, nasal discharge (“snuffles”), pseudoparalysis of an extremity, anemia, thrombocytopenia, and osteochondritis. Late manifestations occur after 2 years of age and may involve the central nervous system, bones, teeth, eyes, and skin.

The diagnosis of syphilis is generally made either with tests that detect the organism directly (e.g., dark-field microscopy or direct fluorescent antibody to *Treponema pallidum* [DFA-TP]) or with serology that detects serum antibodies against the organism (e.g., fluorescent treponemal antibody absorption [FTA-ABS] and *T. pallidum* particle agglutination [TP-PA]) or nontreponemal antibodies generated during infection (e.g., venereal disease research laboratory [VDRL] and rapid plasma reagin [RPR]). However, there is a potential for false-negative serology.

Treatment of syphilis is the same for patients infected or uninfected with HIV, i.e., a penicillin-based regimen with adequate coverage for neurosyphilis. A pregnant woman infected with syphilis must be treated 30 or more days before delivery to effectively prevent perinatal transmission. Careful follow-up is required in all cases, because relapse is more likely in HIV-positive patients.

Mycobacterium tuberculosis
*Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), is not an OI, but it is the most common cause of death of HIV-infected people worldwide. HIV attacks T-lymphocyte cells, the body’s main defense against TB. Therefore, patients with HIV are more susceptible to TB infection. As the HIV epidemic grows,
transmission of TB becomes harder to control. Please refer to the chapter on TB for details regarding the diagnosis and management of its coinfection with HIV.

Preventive therapy against TB includes one or more anti-TB drugs given to HIV-infected patients who have a latent infection with *M. tuberculosis* to prevent progression to active disease. Before considering a patient for preventive therapy, one must exclude active disease. In 1998, the World Health Organization (WHO) and UNAIDS developed recommendations for preventive therapy. Preventive therapy is recommended in areas that have established HIV care and TB control programs. The resources must also be available to:

- distinguish active from latent tuberculosis,
- ensure appropriate monitoring and follow-up,
- ensure a consistent supply of medication, and
- link preventive therapy against TB to voluntary counseling and testing for HIV.

Preventive therapy is recommended for HIV-infected patients with a positive Mantoux skin test who do not have active TB (i.e., have a normal chest radiograph). In areas where skin testing is not feasible, one should consider preventive therapy for the following high-risk patients if they have HIV:

- Persons living in populations with a high prevalence (>30%) of TB infection
- Health care workers
- Household contacts of TB patients
- Prisoners
- Miners

Preventive therapy with isoniazid (INH) is recommended. The dose should be 5 mg/kg of body weight (maximum, 300 mg) by mouth daily for at least 6 months, with clinical monitoring for adverse effects and active TB.

**Table 2. Treatment and prophylaxis dosing for MAC**

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>Prophylaxis</th>
<th>Alternative Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (0-12 years)</td>
<td>Clarithromycin (7.5 mg/kg/dose twice daily) or Azithromycin (10-12 mg/kg/dose once daily) plus Ethambutal (15 mg/kg/day)</td>
<td>Clarithromycin 7.5 mg/kg twice daily</td>
<td>Azithromycin 20 mg/kg by mouth weekly or rifabutin (&gt;6 y/o) 300 mg daily</td>
</tr>
<tr>
<td>Adolescents and adults (&gt;12 years)</td>
<td>Clarithromycin (500 mg twice daily) or Azithromycin (600 mg twice daily) plus Ethambutal (15 mg/kg/day) for at least 12 months</td>
<td>Clarithromycin 500 mg twice daily</td>
<td>Azithromycin 1.2 g by mouth weekly or rifabutin 300 mg daily</td>
</tr>
</tbody>
</table>

* Doses for medications given by mouth

**Table 3. Treatment and prophylaxis dosing for CMV retinitis**

<table>
<thead>
<tr>
<th>Age</th>
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<th>Alternative Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (0-12 years)</td>
<td>Ganciclovir 5 mg/kg IV twice daily for 14 days</td>
<td>Ganciclovir 5 mg/kg IV once daily</td>
<td>Ganciclovir 6 mg/kg IV once daily for 5 days per week</td>
</tr>
<tr>
<td>Adolescents and adults (&gt;12 years)</td>
<td>Ganciclovir 5 mg/kg IV twice daily for 14 days OR Valganciclovir 900 mg orally twice daily for 21 days</td>
<td>Ganciclovir 5 mg/kg IV once daily</td>
<td>Ganciclovir 1000 mg orally 3 times daily or Valganciclovir 900 mg orally once daily</td>
</tr>
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</table>
Opportunistic Infections

*Mycobacterium avium Complex*
*Mycobacterium avium* complex (MAC) occurs all over the world. Symptoms of disseminated MAC are nonspecific and include weight loss or failure to thrive (in children), recurrent fever, abdominal pain, diarrhea, and lymphadenopathy. MAC can be grown in culture, albeit slowly. Acid-fast staining, if available, will be positive. Treatment for MAC requires at minimum a two-drug regimen of either clarithromycin or azithromycin plus ethambutol.

The age and CD4+ lymphocyte count of the patient indicate when to start primary prophylaxis. In adults, prophylaxis is recommended once the CD4+ lymphocyte count is less than 100 cells/µL. In children, CD4+ lymphocyte cell counts vary with age, but if the counts are below 15% for the child’s age group, prophylaxis is recommended.

Once patients receive HAART for at least 6 months and their CD4+ lymphocyte cell counts increase to more than 100 cells/µL (or >200 cells/µL for children aged 2-5 years) for 3 months, one may stop primary prophylaxis. Stop secondary prophylaxis only if the patient has completed at least 12 months of therapy and has maintained a CD4+ lymphocyte cell count of more than 100 cells/µL (or >200 cells/µL for children aged 2-5 years) for 6 months. Currently, stopping prophylaxis is not recommended for children younger than 2 years. See Table 2 for treatment and prophylaxis guidelines.

Viral Infections

*Cytomegalovirus*
*Cytomegalovirus* (CMV) is a common viral infection worldwide. Most people with CMV develop few or no symptoms. However, a fetus exposed to CMV can suffer severe consequences, including mental retardation and even death. In patients with HIV/AIDS, the most common complication of CMV is retinitis (Figure 1). CMV can also cause hepatitis, diarrhea, and encephalitis. CMV retinitis is most commonly seen in patients with CD4+ lymphocyte counts of less than 50 cells/µL and can lead to blindness if untreated. One should advise patients to report to the clinic if they notice changes in their vision, including blurry vision or “floaters.” Many patients are asymptomatic. If possible, patients should have regular fundoscopic examinations (visualizing the deep structures of the eye) to check for changes and if necessary should be referred to an eye specialist.

Ganciclovir intravenously or valganciclovir orally are the antiviral medications recommended for treating CMV. An intraocular form of ganciclovir can be used to treat isolated CMV retinitis. However, using intraocular ganciclovir without adjunctive therapy of a systemic anti-CMV agent increases the incidence of further systemic disease. See Table 3 for the dosing schedule for treatment and posttreatment prophylaxis (also referred to as maintenance therapy). The main side effect of ganciclovir is neutropenia. Other side effects include anemia, thrombocytopenia, and occasionally renal insufficiency. Currently, valganciclovir is not recommended for children.

Recent studies in adults, adolescents, and children older than 12 months suggest that one may discontinue CMV secondary prophylaxis in patients who have maintained a CD4+ lymphocyte cell count of more than 100-150 cells/µL (or 15%) in response to HAART for at least 6 months. If prophylaxis is discontinued, maintain regular ophthalmologic examinations.

*Varicella-Zoster Virus*
Varicella-zoster is the virus that causes chickenpox and shingles in children and adults. Infection with this virus can be much more serious in a person with HIV/AIDS. Infection is spread by aerosolized viral particles. A person is contagious for 24-48 h before a vesicular rash (raised, fluid-filled lesions) is observed and remains contagious until all lesions are crusted over. Diagnosis is mainly clinical.

A vaccine is available to protect patients against this virus. If an HIV-infected child has an age-specific CD4+ lymphocyte percentage greater than 15%, the vaccine may be administered. HIV-infected children require two doses of the varicella vaccine, separated by at least 3 months. If an immunocompromised person comes into contact with someone with varicella, he or she can be protected with varicella-zoster immunoglobulin. Acyclovir, an antiviral medication, decreases the duration of disease. In children, acyclovir can be given intravenously or orally. The pediatric oral dose is 20 mg/kg/dose every 6 h for 5 days. The adult dose is 800 mg four times a day for 5-7 days. Acyclovir can cause pancytopenia (a decrease in all forms of blood cells), particularly when given in conjunction with zidovudine (AZT). Patients must increase the intake of fluids while on acyclovir to avoid crystalluria (the presence of crystals in the urine as a symptom of irritation) and possible acute renal failure.
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Reactivation can cause painful grouped vesicles usually isolated to one dermatome months or years after primary infection. This development is referred to as zoster or shingles. Treatment with acyclovir can lessen the severity.

**Herpes Simplex Virus**

Herpes simplex virus type 1 (HSV-1) and HSV-2 infections also can be severe in patients with HIV/AIDS. HSV can cause ulcers around the mouth, known as cold sores. HSV can cause encephalitis as well.

Diagnosis is mainly clinical. Acute disease usually resolves spontaneously, but treatment for pain associated with the lesions may help the patient feel more comfortable. Genital herpes is a sexually transmitted infection. Using condoms can decrease a patient’s risk of contracting HSV. HSV infection can be transmitted from mother to child, and this occurs at a rate of one case per 2,000-5,000 deliveries. HIV-infected women coinfected with HSV-2 are much more likely to be actively shedding virus at the time of delivery and therefore are at greater risk for transmitting HSV-2 to their infants than are HIV-negative women. Oral or genital herpes can be treated with acyclovir in severe cases. Patients with HSV and HIV/AIDS often have severe recurrent attacks. For these patients, prophylaxis with daily acyclovir can help. The pediatric prophylactic dose is 10 mg/kg/dose twice daily orally. The adult prophylactic dose is 200 mg three times a day or 400 mg twice a day orally.

**Epstein-Barr Virus**

Epstein-Barr virus (EBV) usually causes minor symptoms, much like the common cold or strep throat. However, EBV infection of HIV-infected children can be associated with a pulmonary disease known as lymphoid interstitial pneumonia (LIP). LIP occurs in 20%-30% of HIV-infected children. It usually occurs in children older than 2 years. The diagnosis of LIP is usually made based on clinical criteria; definitive diagnosis requires lung biopsy.

Patients with LIP may initially be asymptomatic. As the disease progresses, they may present with generalized lymphadenopathy, hepatomegaly, and/or digital clubbing. Children may also have nontender, bilateral enlargement of the parotid glands. Respiratory difficulties may become evident because of secondary bacterial infections. In areas where tuberculosis is endemic, one must rule out TB before making a diagnosis of LIP. The chest radiograph associated with LIP will show bilateral diffuse reticulonodular infiltrations and mediastinal lymphadenopathy, which may be confused with TB. Patients often respond well to steroid therapy. Also, antiretroviral treatment can decrease the complications associated with LIP. EBV also has been associated with Burkitt’s lymphoma.

**JC Virus**

JC virus is the virus believed to be associated with progressive multifocal leukoencephalopathy, a disease characterized by altered mental status, limb weakness, or both. Patients may also exhibit personality changes with frequent emotional outbursts. This disease has a course that can vary. It occurs in patients with severe immune suppression and is rarely seen in children. Definitive diagnosis is confirmed by brain biopsy. On an image from computed tomography, one can see diminished density or demyelination (deterioration of the covering of the nerve). There is no treatment for this illness, but strong antiretroviral medications can sometimes improve the symptoms.

**Virus-Associated Malignancies**

**Kaposi Sarcoma**

Kaposi sarcoma is primarily a skin malignancy, but it can also involve internal organs such as the lungs, liver, and spleen. It is associated with the human herpesvirus 8 (HHV-8). Although Kaposi sarcoma has been observed in immunocompetent children in Africa, it is more common in children and adults with HIV/AIDS. In HIV-infected children, the median age of onset of Kaposi sarcoma is 33 months. Kaposi sarcoma associated with HIV/AIDS can present in two forms: mucocutaneous and lymphadenopathic. The mucocutaneous form may be an early type of the lymphadenopathic form. Cutaneous lesions characterizing Kaposi sarcoma can be flat, raised, or nodular and usually are purple or brown. They can occur anywhere on the body, including the palms of the hands, as well as inside the mouth. The most effective treatment for Kaposi sarcoma is antiretroviral therapy. Chemotherapy is often used, particularly when viscera are involved. Limited research also shows that ganciclovir may be associated with reduced disease progression or with lesion regression. Prognosis for Kaposi sarcoma seems to be related to the patient’s overall immune status and the organ systems involved.

HHV-8 can be transmitted through sexual intercourse, blood via needle sharing, and possibly deep kissing (oral secretions). Health providers should counsel HIV-infected
patients to use condoms, not to share needles, and to avoid deep kissing with people infected with HHV-8 or at high risk of infection.

**Human Papillomavirus**

Human papillomavirus (HPV) infects cutaneous and mucosal squamous epithelium. It can cause genital, anal, conjunctival, nasal, oral, and laryngeal warts. In young children, genital warts may be a sign of sexual abuse. However, HPV can be transmitted perinatally. Such transmission is more likely to result in respiratory symptoms from HPV in toddlers (recurrent respiratory palollomatosis). Men who have sex with men have a high prevalence of anal HPV infection.

HPV infection is commonly associated with cervical cancer. Women who are immunocompromised have a higher rate of cervical cancer, as well as a higher rate of recurrence of cervical cancer after treatment. Using condoms can reduce the risk of transmission of sexually transmitted infections and may reduce the risk of transmitting HPV. Women with HIV should have a Papanicolaou (Pap) smear every 6 months for the first year after diagnosis of HIV. If these smears are negative, women with no other risk factors for cervical cancer should have a Pap smear once a year.

A vaccine for HPV is now available in some settings. This vaccine is safe for use in HIV-infected women and recommended in all women and female youth aged 9-26 years for prevention of HPV and cervical cancer. Multiple treatments for HPV-associated skin and external lesions are available. Specific treatments must be catered to the circumstances of the patient.

**Parasitic Infections**

**Pneumocystis jirovecii**

*Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) is an organism that does not cause illness in immunocompetent hosts. However, it can cause severe pneumonia in patients with HIV/AIDS. This infection is prevalent worldwide. One should suspect *Pneumocystis jirovecii* pneumonia (formerly called PCP) in patients with tachypnea (increased rate of respiration), cough, and shortness of breath. Lung auscultation (sounds) may be normal because rales and rhonchi may develop late in the clinical course. Patients are commonly hypoxic with a normal chest radiograph. The chest radiograph may show bilateral interstitial infiltrates (Figures 2 and 3). Children can be severely ill with this disease, and it is often the first AIDS-defining illness in a child. Definitive diagnosis requires identifying the organism, usually from a bronchoalveolar lavage (a washing that can retrieve cells or tissue from the lungs and the alveoli in them) or an induced sputum sample. PCP is best treated with TMP-SMX.

![Figure 2. Chest x-ray](image)

*Chest radiograph and biopsy of a 2-year-old boy with HIV infection and Pneumocystis jiroveci pneumonia. Note the presence of bilateral interstitial lung disease, pneumomediastinum, and subcutaneous emphysema. Gomori-methenamine silver stain shows numerous dark-staining cysts of Pneumocystis jiroveci.*

![Figure 3. Biopsy](image)
The WHO recommends TMP-SMX primary and secondary prophylaxis for all symptomatic people with HIV and particularly in resource-limited settings where bacterial infections and malaria are prevalent among people living with HIV. For prevention of PCP and toxoplasmosis, the WHO recommends TMP-SMX for adults with CD4 counts less than 350 cells/µL or WHO stage 2, 3, and 4. The WHO recommends TMP-SMX prophylaxis for children according to age:

- Younger than 1 year, irrespective of CD4 cell count
- 1-5 years old, symptomatic children (WHO stages 2-4) or CD4 less than 25%
- 6 years or older who are symptomatic (WHO stages 2-4) or CD4 cell count <350 cells/µL

Infants born to HIV-infected mothers should begin PCP prophylaxis when they are 4-6 weeks of age and should remain on prophylaxis until they are 12 months old or until it can be determined definitively whether they are HIV infected, taking into account the ongoing risk of exposure to HIV via breast-feeding. If they are HIV infected, their treatment should follow the guidelines for HIV-infected children.

Guidelines in the United States recommend initiation of primary prophylaxis if the CD4 cell count falls below 200 cells/µL or 15% for children younger than 6 years. See Table 4 for dosing guidelines.

Primary treatment of PCP includes TMP-SMX 15-20 mg TMP/kg/day divided every 6-8 h for 21 days, plus steroid therapy for severe disease. Supplemental oxygen should be given if needed. The prophylaxis dose (Table 4) for adults is TMP 160 mg and SMX 800 mg once a day orally for 3 consecutive days a week. If this regimen is not tolerated, one may use half the dose instead. Some patients are given the full dose every day; this will also protect them against toxoplasmosis. The dose for children is TMP 150 mg/m² of body surface area and SMX 750 mg/m² in two divided doses three consecutive days a week. As in adults, this may be given to children every day to protect against toxoplasmosis. If patients cannot tolerate TMP-SMX, have G6PD (glucose-6-phosphate dehydrogenase) deficiency (an enzyme disorder affecting red blood cells), are allergic to sulfa drugs, or experience side effects, dapsone may be used. The main side effect of TMP-SMX is rash. As with all sulfonamides, TMP-SMX can on rare occasions cause agranulocytosis (destruction of certain white blood cells), aplastic anemia (loss of bone marrow production), other blood disorders, Stevens-Johnson syndrome (a severe allergic reaction characterized by breakdown of mucous membranes), and hepatic necrosis (death of liver cells), or interstitial nephritis. The dose of dapsone for adults is 100 mg once daily. For children, the recommended dose is 2 mg/kg daily, with a maximum dose of 100 mg/day. Other alternative drugs include clindamycin-primaquine, dapsone-trimethoprim, atovaquone, pentamidine isethionate, and trimetrexate glucuronate.

Both primary and secondary prophylaxis can be discontinued in adults and adolescents who have maintained a CD4+ lymphocyte cell count of more than 200 cells/µL for at least 3 months after 6 months of HAART. Children older than 1 year may discontinue primary or secondary prophylaxis if their CD4 cell count remains above 15% for 3 months after 6 months of HAART. The WHO recommends stopping primary or secondary prophylaxis when two consecutive CD4 counts are greater than 200 cells/µL and the patient is on antiretroviral therapy for more than 6 months with good adherence once a child is older than 5 years. One should reinitiate prophylaxis if the CD4 cell count falls below 200 cells/µL or 15%. Malaria-endemic areas and/or places where CD4 cell counts are not regularly available may continue TMP-SMX prophylaxis indefinitely in HIV-infected children.

### Table 4. Prophylaxis for PCP – Once-daily dosing

<table>
<thead>
<tr>
<th>Weight</th>
<th>Suspension: 40 mg TMP + 200mg SMX/5ml</th>
<th>Tablets (SS): 80 mg TMP/400mg SMX</th>
<th>Tablets (SS): 160 mg TMP/800mg SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 kg</td>
<td>2.5 ml</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5-8 kg</td>
<td>5 ml</td>
<td>1/2 tab</td>
<td>–</td>
</tr>
<tr>
<td>9-16 kg</td>
<td>10 ml</td>
<td>1 tab</td>
<td>1/2 tab</td>
</tr>
<tr>
<td>17-50 kg</td>
<td>20 ml</td>
<td>2 tabs</td>
<td>1 tab</td>
</tr>
<tr>
<td>&gt; 50 kg</td>
<td>20 ml</td>
<td>2 tabs</td>
<td>1 tab</td>
</tr>
</tbody>
</table>
**Cryptosporidium**

*Cryptosporidium* is a parasite that causes persistent diarrhea and cholecystitis (gall bladder inflammation) in immunocompromised patients. Cryptosporidium is spread by direct contact with infected adults, children in diapers or of the age to be in diapers, and infected animals. Food and water contaminated with feces can spread infection as well. People with HIV/AIDS should be careful when coming in contact with human feces (e.g., changing diapers) or animal feces, as well as when working with the soil. Good hand washing and boiling water when advised are important for preventing infection.

Patients with cryptosporidiosis will have frequent, watery, voluminous stools, often lasting longer than 2 weeks. They also may experience abdominal cramping. If the biliary system (gall bladder and biliary ducts) is involved, they also may have nausea and right-upper-quadrant abdominal pain. Cryptosporidia in stool can be seen under a microscope with a modified acid-fast staining method. Nitazoxanide effectively treats cryptosporidiosis in immunocompetent patients. Dosing for adults is 500 mg by mouth twice daily for 3 days. Children aged 12-47 months should receive 100 mg by mouth twice daily for 3 days; children aged 4-11 years should receive 200 mg by mouth twice daily for 3 days; and those aged 12 years and older should receive the adult dose. Nitazoxanide was ineffective in HIV-infected children; however, one may consider an extended course of 6 days because in more immunocompetent children this dose may lessen the course of illness. Metronidazole and azithromycin have been used to treat *Cryptosporidium* with various degrees of success. Effective HAART is the recommended treatment for *Cryptosporidium* infections.

**Isospora belli**

*Isospora belli* spreads by the same routes of transmission as *Cryptosporidium* and has the same symptoms. *Isospora* can be diagnosed on acid-fast stain of stool. TMP-SMX can treat *Isospora*, but there is a 50% relapse rate among adults. Prophylaxis with TMP-SMX may be needed to prevent relapses. The dosing and side effects of TMP-SMX for *Isospora belli* are the same as for *Pneumocystis jirovecii* (Table 4).

**Malaria**

Malaria is a disease caused by several species of *Plasmodium*, a parasite transmitted via mosquito bites. It is found primarily in tropical regions of the world. About 90% of malaria cases occur in sub-Saharan Africa, which poses substantial problems because HIV prevalence there is also high. The two infections can have several harmful interactions.

Pregnant women with HIV infection are at increased risk of malaria. HIV increases the chances of placental malaria, which is associated with a greater risk of HIV transmission to the infant, low birth weight, and mortality. Patients suffering from AIDS (and possibly young children) are at increased risk of symptomatic malaria. They may present with a higher parasite burden. A study in Malawi suggests that malaria infection might increase HIV viral load.

Prevention is the mainstay of malaria reduction in many areas. One of the most effective prevention strategies is the use of insecticide-treated nets (ITNs) over the bed. ITN use decreases pediatric morbidity and mortality from malaria. Most nets need to be retreated with insecticide every 6 months. Wearing long sleeves and long pants can also prevent infection. So can remaining indoors at dawn and dusk, the times of highest transmission risk. Intermittent prophylaxis with medication for pregnant women and children is being studied. Finally, community efforts to eliminate or cover standing water can prevent mosquito breeding. A combination of TMP-SMX and ITNs is associated with a marked reduction in malaria incidence among HIV-infected persons.

Proper treatment of malaria is imperative to minimize morbidity and mortality. Different regions of the world have different types of malaria, some of which can be drug resistant. Treatment regimens for a particular setting depend on national guidelines. Examples of drugs used to treat malaria are chloroquine, quinine, primaquine, mefloquine, pyrimethamine-sulfadoxine, and atovaquone plus proguanil.

**Toxoplasma gondii**

*Toxoplasma gondii* is transmitted via raw or undercooked meat, particularly pork, lamb, and venison. It also can be transmitted via cat feces. Meat should be thoroughly cooked, and immunosuppressed individuals should avoid
contact with stray cats and cat feces. Good hand washing can prevent infection.

Toxoplasmosis in the immunocompromised host usually causes central nervous system disease, specifically brain abscesses. Toxoplasmosis commonly reactivates, causing repeated infections. Patients have focal neurologic deficits, including seizures, hemiparesis, hemiplegia, cerebellar tremor, cranial nerve palsies (e.g., unilateral facial droop), hemisensory loss, visual problems or blindness, personality changes, and cognitive disorders. Severe localized headache that does not respond to analgesics may be present. *Toxoplasma gondii* infection is classically seen as multiple-ring enhancing lesions on a computed tomography scan. Antibodies often can be detected in the blood or other body fluids (cerebrospinal fluid). This disease is much more common in adults than in children. However, infants infected in utero are at high risk for toxoplasmosis encephalitis.

Treat toxoplasmosis with pyrimethamine and sulfadiazine. Treatment for toxoplasmosis should continue for at least 4 weeks after complete resolution of disease. See Table 5 for treatment and secondary prophylaxis guidelines. Folinic acid is usually also given during treatment because pyrimethamine inhibits folate metabolism. Alternative treatment and secondary prophylaxis regimens include pyrimethamine-clindamycin, pyrimethamine-azithromycin, and pyrimethamine-atovaquone. However, one should use these combinations only when the risks of using pyrimethamine-sulphadiazine outweigh the benefits. Limited data also support using alternative regimens in children. Primary prophylaxis is recommended with TMP-SMX daily for severely immunocompromised patients (see Table 4 for dosing guidelines).

Patients who have experienced an increase in CD4+ lymphocyte cell count after at least 6 months of HAART to more than 200 cells/µL (or >15%) for at least 3 months may stop primary prophylaxis for toxoplasmosis. One may discontinue secondary prophylaxis if a patient maintains a CD4+ cell count of more than 200 cells/µL for at least 6 months. The WHO recommends stopping primary or secondary prophylaxis when two consecutive CD4 counts are greater than 200 cells/µL and the patient is on antiretroviral therapy for more than 6 months with good adherence and is older than 5 years.

### Fungal Infections

*Candida albicans*

*Candida albicans* is the most common fungal infection diagnosed in HIV-infected patients. Oral candidiasis (also called thrush) is particularly common. It is often one of the presenting signs of HIV infection in patients who do not have other reasons (e.g., recent antibiotic use) to have fungal disease. Patients have white or yellow plaques on the oropharyngeal mucosa and on the tongue. If esophageal infection is also present, the patient may complain of inability to swallow or retrosternal chest pain when swallowing. Infants may begin to feed and then stop after the first few swallows, arching their backs and

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**Table 5. Treatment and secondary prophylaxis for Toxoplasma gondii**

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment</th>
<th>Secondary Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (0-12 years)</td>
<td>Pyrimethamine: 1-2 mg/kg/day orally for 2 days, then 1 mg/kg/day orally for 2 months, then 1 mg/kg/day orally 3 days/wk (maximum 50 mg) AND Sulfadiazine: 100 mg/kg oral loading dose, then 50 mg/kg twice daily by mouth AND Folinic acid: 5-10 mg orally or intramuscularly 3 times a week</td>
<td>Pyrimethamine: 1 mg/kg orally daily (maximum 25 mg) AND Sulfadiazine: 40 mg/kg/day orally 3 times a day AND Folinic acid: 5 mg orally every 3 days</td>
</tr>
<tr>
<td>Adolescents and adults (&gt;12 years)</td>
<td>Pyrimethamine: 200 mg orally in divided doses, then 50 mg orally daily AND Sulfadiazine: 2000 mg orally 3 times daily AND Folinic acid: 15 mg orally daily</td>
<td>Pyrimethamine: 25 mg orally daily AND Sulfadiazine: 1000 mg orally 3 times a day AND Folinic acid: 15 mg orally daily</td>
</tr>
</tbody>
</table>
Opportunistic Infections

turning their heads because of difficulty in swallowing. Patients who are critically ill, have been treated with long-term systemic antibiotics, or have an indwelling catheter (e.g., central venous access device) may develop systemic candidiasis or candidemia. Diagnosis is mainly clinical; however, potassium hydroxide preparation can be used for microscopic demonstration of pseudohyphae. One can treat oral candidiasis with gentian violet applied directly to the lesions or with nystatin (or other topical antifungals) in liquid or tablet form taken orally. If one suspects candidal esophagitis, treat with ketoconazole or fluconazole. Treat vaginal candidiasis with topical antifungal agents.

Amphotericin B can treat systemic candidiasis that does not respond to other antifungal agents. The dose of amphotericin B will depend on the severity of the illness, ranging from 0.5 mg/kg/day to 1.5 mg/kg/day. Patients who receive this drug should be monitored when they are in the hospital. Administration of amphotericin B can be associated with shaking chills or rigors during infusion. Amphotericin B also causes hypokalemia (decreased potassium in the serum), bone marrow suppression, and nephrotoxicity.

Prophylaxis is recommended only for frequent and severe recurrences of candidiasis. The Centers for Disease Control and Prevention recommends daily fluconazole for prophylaxis of frequent and severe recurrences of candidiasis. However, daily fluconazole treatment can lead to the development of fluconazole-resistant candidiasis. An alternative is to use daily nystatin for prophylaxis, particularly for oral thrush. The prophylaxis dose of fluconazole is the same as the treatment dose, according to the Centers for Disease Control and Prevention recommendations: for adults, 100-200 mg by mouth once a day; for children, 3-6 mg/kg by mouth once daily. The dose for nystatin prophylaxis is the same as the treatment dose (Table 6).

Cryptococcosis

Cryptococcosis usually occurs in HIV-infected patients with severe immune suppression and most commonly causes cryptococcal meningitis. Mortality during the first 6 weeks after diagnosis can be as high as 20%. Clinical signs and symptoms of this infection can be subtle. The most common clinical manifestation is indolent fever. Patients may have headache and altered mental status. Cutaneous manifestations can mimic molluscum contagiosum. These symptoms usually evolve over weeks or months. Meningismus (irritation of the brain and spinal cord without inflammation) as well as signs and symptoms of increased intracranial pressure may be present. Diagnosis is made by India ink preparation of spinal fluid, testing spinal fluid and/or serum for cryptococcal antigen, or spinal fluid culture. Cryptococcal meningitis is often associated with a high opening pressure on spinal tap. It is also fatal without treatment. Treatment is usually amphotericin B plus flucytosine for 2 weeks, followed by fluconazole (400 mg/day for 8-10 weeks). The WHO recommends initial treatment with amphotericin B for 2 weeks followed by itraconazole or fluconazole for 8 weeks and maintenance therapy with itraconazole or fluconazole. Monitor patients for increased intracranial pressure, particularly in the first 2 weeks of treatment.

After initial treatment, secondary prophylaxis with fluconazole is recommended for both adults and children. The doses are the same as the maximum doses listed for candidiasis (Table 6).

Adults, adolescents, and children older than 6 years appear to be at low risk for recurrence of cryptococcosis if they have completed primary treatment, remained asymptomatic, and maintained a CD4+ lymphocyte cell count greater than 100-200 cells/µL for more than 6 months. Some experts would recommend a repeat

| Table 6. Recommended dosing for prevention of severe and recurrent candidiasis |
|---|---|---|
| Age | Nystatin Dose | Fluconazole Dose |
| Neonates (<1 month) | 100 000 units 4 times daily by mouth | 3-6 mg/kg by mouth every 72 hours (if ≥14 days old, use infant dose) |
| Infants (1-12 months) | 200 000 units 4 times daily by mouth | 3-6 mg/kg by mouth daily |
| Children (1-12 years) | 400 000 units 4 times daily by mouth | 3-6 mg/kg by mouth daily |
| Adults (>12 years) | 400 000-600 000 units 4 times daily by mouth | 100-200 mg by mouth daily |
evaluation of cerebrospinal fluid to document a negative culture in an asymptomatic patient prior to stopping prophylaxis. Reinitiate prophylaxis if the CD4 cell count again falls below 200 cells/µL.

**Histoplasmosis**

*Histoplasma capsulatum* is a fungus endemic to certain parts of the United States, Latin America, and other parts of the world. In endemic areas, more than 25% of HIV-infected patients develop disseminated histoplasmosis. *H. capsulatum* can infect the lungs and the oropharyngeal and gastrointestinal tract as well as skin, brain, adrenal glands, and bone marrow. Patients may present with fever and weight loss, lymphadenopathy, splenomegaly, and diarrhea or abdominal pain. Some HIV-infected patients may present with intestinal ulcers. Those with pulmonary infection may be asymptomatic or may present with dyspnea. A chest radiograph will be abnormal in 70% of patients with histoplasmosis. A radiograph may show diffuse interstitial or reticulonodular infiltrates.

One can use culture, antigen testing, or fungal stain of the tissues to make the diagnosis. Depending on the site of infection, patients may present with anemia, leukopenia, elevated hepatic enzymes, or an elevated serum lactate dehydrogenase level. Treatment is with amphotericin B (0.7-1 mg/kg/day) initially, followed by itraconazole 200 mg once or twice daily. Itraconazole is more effective than ketoconazole or fluconazole. Treatment may last for up to 1 year. In patients with CD4+ lymphocyte counts of less than 150 cells/µL, lifelong maintenance therapy is recommended at the same dose of itraconazole. Itraconazole can interact with many different medications, including rifampin, so it must be monitored.

**References**


