

# X: DIAGNOSIS AND TREATMENT OF OPPORTUNISTIC INFECTIONS (OIs) AMONG HIV-EXPOSED AND -INFECTED CHILDREN\*

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\*This chapter has been adapted for use in the Caribbean from the 2004 U.S. Centers for Disease Control (CDC)/National Institutes of Health (NIH)/Infectious Disease Society of America (IDSA) Guidelines for the Treatment of Opportunistic Infections in HIV-Exposed and -Infected Children (CDC. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Weekly [serial on the Internet] 3 Dec 2004;53[RR14]:1-63.) Last accessed 2005. Available at: [www.cdc.gov/mmwr](http://www.cdc.gov/mmwr)).

## **X. DIAGNOSIS AND TREATMENT OF OPPORTUNISTIC INFECTIONS (OIs) AMONG HIV-EXPOSED AND -INFECTED CHILDREN**

### **INTRODUCTION**

Opportunistic infections (OIs) remain a frequent cause of morbidity and mortality in HIV-infected children in the Caribbean.<sup>1</sup> The major conditions causing paediatric OIs include *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia (PCP), tuberculosis (TB), cytomegalovirus (CMV) infection, gastroenteritis, persistent recurrent diarrhoea, and serious and recurrent bacterial infections causing pneumonia and meningitis.

The management of OIs in children differs from that in adults in several key respects. OIs in children usually reflect primary acquisition of the pathogen, whereas in adults, disease typically occurs as a consequence of re-activation of a pathogen acquired prior to HIV infection. In children with perinatally-acquired HIV infection, OIs are usually acquired in immature and already compromised immune systems. Laboratory diagnosis of paediatric OIs is complicated by the relative difficulty of adequate specimen collection in infants and children. Treatment recommendations must consider differences in paediatric dosing, formulation, drug pharmacokinetics, administration, and toxicities. Finally, HIV-infected pregnant women co-infected with opportunistic pathogens may be more likely to transmit these infections to their infants than are women who are HIV-uninfected. As such, these guidelines also address congenitally-acquired OIs that develop in HIV-uninfected infants born to HIV-infected mothers.

The Caribbean reflects a wide diversity of access to appropriate diagnostic and treatment options for paediatric OIs. Although it currently may not be possible to implement specific testing and treatment options in every setting, this document is written to present optimal tools for the future identification, care, and treatment of OIs in HIV-exposed and -infected children. Caribbean nations presently obtain funding for HIV/AIDS and OI care from various sources and are at varied stages of scaling up care and treatment plans for paediatric OI management. Thusly, these guidelines must be interpreted, implemented, and further adapted for use in light of available facilities in each Caribbean territory.

### **DISEASE-SPECIFIC RECOMMENDATIONS**

#### **PNEUMOCYSTIS JIROVECI (FORMERLY CARINII) PNEUMONIA (PCP)**

##### ***Epidemiology***

*P. jiroveci*, a fungus susceptible to antiprotozoal agents, causes *Pneumocystis* pneumonia (PCP). *P. carinii* now refers to the organism that is found only in rats.

*P. jiroveci* is usually acquired in childhood; serum antibodies are found in more than 80% of children by age two to four years. Most HIV-uninfected infants with *P. jiroveci* infection will have either mild respiratory symptoms or remain completely asymptomatic.

PCP remains the most common AIDS-indicator disease in HIV-infected children. Its incidence varies among countries and ranges from 5.4% in Jamaican children who are primarily on PCP prophylaxis<sup>2</sup> to 23% in Puerto Rico<sup>3</sup> and 37.5% of AIDS cases in children in Barbados.<sup>4</sup>

The highest incidence of PCP in HIV-infected children is in the first year of life, with cases peaking at age three to six months. Mortality is high with PCP and is identified as the primary cause of death in up to 70% of HIV-infected children in Barbados, as reported in the national surveillance system prior to the availability of HAART therapy.<sup>5</sup>

Unlike in older children and adults, CD4+ T cell counts are not a good indicator of risk for PCP in infants age one year or younger; many young infants with PCP have CD4+ T cell counts of  $>1,500$  cells/mm<sup>3</sup>, and counts can drop very rapidly shortly before PCP develops in infants.

### ***Clinical Manifestations***

Clinical features of PCP in HIV-infected children are similar to those in adults. Fever, tachypnea, dyspnoea, and cough are seen most commonly, especially in the younger child. Onset can be abrupt or may be insidious in the older child with non-specific symptoms such as mild cough, dyspnoea, poor feeding, and weight loss. Almost all children will have tachypnea by the time pneumonitis is seen on chest radiograph. Bibasilar rales with evidence of respiratory distress may be heard on physical examination. Most children with PCP have significant hypoxia with low arterial oxygen pressure [pO<sub>2</sub>] and an alveolar-arterial oxygen gradient [(A-a)DO<sub>2</sub>] of  $\geq 30$ mmHg.

Chest radiographs most commonly show bilateral diffuse parenchymal infiltrates with “ground-glass” or reticulogranular appearance, but they also may be normal or show only mild parenchymal infiltrates. The earliest infiltrates are perihilar, progressing peripherally but sparing the apical portions of the lung until last. Lobar, cavitory, nodular, or miliary lesions; pneumothorax; or pneumomediastinum are seen rarely.

Infants with dual infection with CMV and PCP may have more severe pneumonic disease, and they are more likely to require assisted ventilation (in countries where available), receive corticosteroids, or die than those with PCP alone.

### ***Diagnosis***

Definitive diagnosis of PCP requires demonstration of the organism in pulmonary tissues or fluids. Diagnostic procedures are the same as those used for adults with suspected PCP, but some procedures may be more difficult to perform in children. Induced sputum analysis, bronchoscopy with bronchoalveolar lavage (BAL), fiberoptic bronchoscopy with transbronchial biopsy, and open-lung biopsy are not uniformly available throughout the Caribbean. If possible, a specific diagnosis should be sought rather than relying on presumptive diagnosis.

When an appropriate sample is available, three types of stains may be used to diagnose *P. jiroveci* organisms in specimens. Gomori’s methenamine-silver stain stains the cyst wall brown or black. Toluidine Blue stains the cyst wall blue or lavender and also stains fungal elements. Giemsa or Wright’s stains stain the trophozoites and intracystic sporozoites pale blue with a punctate red nucleus. Unlike the other stains, this does not stain the cyst wall.

### ***Treatment Recommendations***

Trimethoprim-sulfamethoxazole (TMP-SMX; co-trimoxazole) is the treatment of choice for PCP. For severe disease requiring hospitalisation, TMP-SMX should initially be given intravenously. After the acute pneumonitis has resolved, children with mild to moderate disease who do not have malabsorption or diarrhoea may switch to oral treatment to complete a twenty-one-day course.

For patients intolerant of TMP-SMX or who demonstrate clinical treatment failure after five to seven days of TMP-SMX therapy, the alternative treatment of choice is intravenous pentamidine isothionate. Additional alternative treatments shown to be effective for mild to moderate PCP disease have limited data in children but include clindamycin/primaquine, atovaquone suspension, and dapsone-TMP. There is no evidence for synergistic or additive effects on efficacy of these agents; therefore, due to potential increased toxicity, their combined use with TMP-SMX would not be recommended.

Based on studies in adults, a short course of corticosteroids may be indicated in cases of PCP of moderate or great severity if started as early as possible and within seventy-two hours of diagnosis. Several small studies have shown reduction in acute respiratory failure, decreased need for ventilation, and decrease in mortality with early use of corticosteroids in HIV-infected children with PCP. Indications for corticosteroid use include a pO<sub>2</sub> value of  $<70$ mmHg or (A-a)DO<sub>2</sub> of  $>35$ mmHg.

### ***Monitoring and Adverse Events***

Adverse reactions to TMP-SMX reported in children include rash (including erythema multiforme and rarely Stevens-Johnson syndrome); haematologic abnormalities such as neutropaenia, thrombocytopenia, megaloblastic or rarely aplastic anaemia; gastrointestinal complaints (generally mild); hepatitis; and renal disorders such as interstitial nephritis. The overall frequency of adverse reactions appears to be lower in HIV-infected children than in adults; only about 15% of children have significant adverse reactions to TMP-SMX. For mild or moderate skin rash, TMP-SMX can be temporarily discontinued and restarted once the rash has resolved. If an urticarial rash or Stevens-Johnson syndrome occurs, TMP-SMX should be discontinued and not re-administered.

Serious adverse reactions to intravenous pentamidine have been reported in approximately 17% of children. Use of intravenous pentamidine can cause renal toxicity but can be averted by adequate hydration and careful monitoring of renal function and electrolytes. Severe hypotension (particularly if infused rapidly), prolonged QT interval, and cardiac arrhythmias also can occur. Hypoglycaemia (usually after five to seven days of therapy) or hyperglycaemia, hypercalcaemia, hyperkalaemia, pancreatitis, and insulin-dependent diabetes mellitus have also been reported. A metallic or bitter taste may be experienced.

Primaquine is contra-indicated in patients with glucose-6-dehydrogenase deficiency due to possibility of inducing haemolytic anaemia. Primaquine, atovaquone, and dapsone may cause skin rashes, nausea, and diarrhoea. Atovaquone and dapsone may also cause an increase in liver enzymes. The primary adverse reaction to dapsone is reversible neutropaenia, although anaemia and thrombocytopenia have been observed.

### ***Prevention of Recurrence***

In HIV-infected children, lifelong suppression is indicated following treatment for PCP to prevent recurrence; details on secondary prophylaxis (maintenance therapy) are provided in *Chapter VI.: Recommendations for Adult and Paediatric Opportunistic Infections Prophylaxis*. The safety of discontinuation of secondary prophylaxis following immune reconstitution with HAART in children has not been studied extensively.

## ***TOXOPLASMOSIS***

### ***Epidemiology***

The major mode of *Toxoplasma gondii* acquisition in infants and young children is congenital, occurring almost exclusively among neonates born to women with primary toxoplasmosis during pregnancy.\* In 1986, the seroprevalence of *T. gondii* was 57% in pregnant Jamaican women.<sup>6</sup> Congenital infection in the Caribbean has been associated with severe pathology, most often resulting in chorioretinitis.<sup>7</sup>

Older children, adolescents, and adults typically acquire *T. gondii* infection by eating poorly cooked meat that contains parasitic cysts or by accidentally ingesting sporulated oocysts in soil or contaminated food or water. Serosurveys performed in school-aged children from the Upper Leeward Islands (Saba, St. Maarten, St. Eustatius, Netherland Antilles), Guadeloupe, and Jamaica have shown evidence of *T. gondii* antibodies in 45.5% to 55% of children.<sup>8</sup>

AIDS-defining infection of the central nervous system (CNS) with *T. gondii* is uncommon in HIV-infected children, being reported as an AIDS-indicator condition in less than 2% of paediatric AIDS cases in Jamaica.<sup>9</sup>

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\*The incidence of *T. gondii* transmission from a mother with **chronic** *T. gondii* infection to her infant is uncommon (<4%). A few cases have been reported of mother-to-infant *T. gondii* transmission from mothers with chronic *T. gondii* infection who were also HIV-infected, presumably due to re-activation of chronic infection secondary to severe immune suppression; however, this has not been documented in the Caribbean.

### ***Clinical Manifestations***

Most infants with congenital toxoplasmosis (70% to 90%) are asymptomatic at birth but are more likely than symptomatic infants to develop late sequelae such as chorioretinitis, visual impairment, and intellectual and/or neurologic impairment, months to years after infection. Predominantly neurologic disease or generalised disease occurs in those infants who are symptomatic at birth. Symptoms may include maculopapular rash, generalised lymphadenopathy, hepatosplenomegaly, jaundice, haematologic abnormalities, and significant CNS disease including hydrocephalus, intracerebral calcification, microcephaly, chorioretinitis, and seizures.

Similarly, toxoplasmosis acquired after birth is most often initially asymptomatic. When symptoms ultimately develop, they are frequently nonspecific and may include malaise, fever, sore throat, myalgia, lymphadenopathy (cervical), and/or a mononucleosis-like syndrome featuring a maculopapular rash and hepatosplenomegaly. Toxoplasmosis may also present as ocular disease, pneumonitis, hepatitis, and cardiomyopathy/myocarditis. *T. gondii* encephalitis should be considered in all HIV-infected children with fever and new neurologic findings such as reduced alertness or seizures. Focal findings on neurologic exam are typical.

### ***Diagnosis***

HIV-infected women may be at increased risk of transmitting *Toxoplasma* to their foetuses and serologic testing for *Toxoplasma* should be performed on all HIV-infected pregnant women. All infants whose mothers are both HIV-infected and seropositive for *Toxoplasma* should be evaluated for congenital toxoplasmosis by using an enzyme immuno-assay or an immunosorbent assay to detect the presence of *Toxoplasma*-specific IgM, IgA, or IgE in neonatal serum within the first six months of life or persistence of specific IgG antibody beyond age twelve months. IgA may be more sensitive for detection of congenital infection than IgM or IgE. However, approximately 20% to 30% of infants with congenital *Toxoplasmosis* will not be identified in the neonatal period with IgA or IgM assays.

If there is uncertainty regarding a possible diagnosis of congenital toxoplasmosis at the time of delivery, an evaluation of the neonate should be undertaken and should include the following: ophthalmologic, auditory, and neurologic examinations; lumbar puncture; and imaging of the head (either CT or MRI scan) to determine whether hydrocephalus or calcifications are present.

A presumptive diagnosis of CNS toxoplasmosis is based on clinical symptoms, serologic evidence of infection, and the presence of a space-occupying lesion on imaging studies of the brain. A negative serology does not exclude that diagnosis. A CT scan of the brain may show multiple, bilateral, ring-enhancing lesions in CNS toxoplasmosis, especially in the basal ganglia and cerebral corticomedullary junction. MRIs are more sensitive and will confirm basal ganglia lesions in nearly all patients.

Definitive diagnosis of *Toxoplasma* encephalitis requires histologic or cytologic confirmation by brain biopsy, which may demonstrate leptomenigeal inflammation, microglial nodules, gliosis, and *Toxoplasma* cysts. Biopsy is usually reserved for patients with early neurologic deterioration despite empiric treatment or for children who fail to respond to anti-*Toxoplasma* appropriate therapy.

### ***Treatment Recommendations***

If an HIV-infected woman has a symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered, irrespective of whether the mother was treated during pregnancy.

The preferred treatment for congenital toxoplasmosis is twelve months of pyrimethamine plus sulfadiazine with supplementary leucovorin (folinic acid) to minimise pyrimethamine-associated haematologic toxicity.

HIV-infected children with acquired CNS, ocular, or systemic toxoplasmosis should be treated with the same combination for six weeks assuming clinical and radiological improvement. Clindamycin can be

used in patients who develop sulfonamide hypersensitivity. Longer courses of treatment may be required in cases of extensive disease or poor response after six weeks of treatment.

Alternative regimens studied in adults but not in children include: TMP-SMX alone; atovaquone plus pyrimethamine and leucovorin as above; atovaquone with sulfadiazine alone; and atovaquone as a single agent in patients intolerant to both pyrimethamine and sulfadiazine.

Corticosteroids (e.g. dexamethasone or prednisone) have been used in children with CNS disease when cerebrospinal fluid (CSF) protein is very elevated (e.g. >1,000 mg/dL) or with focal lesions with significant mass effects. Because of the potential immunosuppressive effects of steroids, they should be discontinued as soon as possible.

### ***Monitoring and Adverse Events***

Pyrimethamine can be associated with rash (including rarely Stevens-Johnson syndrome) and nausea. Its primary toxicity is reversible bone marrow suppression (neutropaenia, anaemia, and thrombocytopaenia). A complete blood count should be performed at least weekly while the child is on daily pyrimethamine and at least monthly while on less than daily dosing. Leucovorin (folinic acid) should always be administered with pyrimethamine; increased doses of leucovorin may be required in the event of marrow suppression. Because of the long half-life of pyrimethamine, leucovorin should be continued one week after pyrimethamine has been discontinued.

Adverse effects of sulfadiazine include rash, fever, leukopaenia, hepatitis, gastrointestinal symptoms (nausea, vomiting, diarrhoea), and crystalluria.

### ***Prevention of Recurrence***

In HIV-infected children, lifelong suppression is indicated following treatment for toxoplasmosis to prevent recurrence; details on secondary prophylaxis (maintenance therapy) are provided in *Chapter VI.: Recommendations for Adult and Paediatric Opportunistic Infections Prophylaxis.* The safety of discontinuation of secondary prophylaxis following immune reconstitution with HAART in children has not been studied extensively.

## ***CRYPTOSPORIDIOSIS/MICROSPORIDIOSIS***

### ***Epidemiology***

*Cryptosporidium* species, such as *C. hominis*, *C. parvum*, and *C. meleagridis*, are protozoal parasites that mainly cause enteric illness in humans and animals. These parasites invade the gut mucosa, causing severe profuse, nonbloody, watery diarrhoea leading to dehydration and malnutrition in immunocompromised hosts. Diarrhoea is often more prolonged with cryptosporidiosis than with other intestinal parasites.<sup>10</sup>

The parasite is transmitted by ingestion of oocysts excreted in the faeces of infected animals and humans. Person-to-person transmission is common among young children, and foodborne spread can also occur. Infection is endemic in Caribbean children and occurs most frequently in those age two years or younger.<sup>11</sup> Oocysts have been identified in up to 17% of Haitian children age two years or younger with acute diarrhoea.<sup>12</sup> Cryptosporidiosis has been reported in 4% to 8% of stool samples from children age nine years or younger in Jamaica and Cuba, respectively.<sup>13</sup>

*Microspora* species are obligate, intracellular, spore-forming protozoa that in children primarily cause moderate to severe diarrhoea. *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common microsporidia that cause infection in patients with HIV infection. *E. bieneusi* is not associated with disseminated disease.

*Microspora* parasites develop in enterocytes and are excreted with faeces, and like *C. parvum*, are transmitted by the faecal-oral route, which can include ingestion of contaminated food or water.

### ***Clinical Manifestations***

Frequent, persistent, watery, and generally nonbloody diarrhoea is the most common manifestation of both cryptosporidial and microsporidial infections, with abdominal cramps, fatigue, vomiting, anorexia, and weight loss/poor weight gain. Fever and vomiting are also relatively common in children, mimicking viral gastroenteritis.

In immunocompromised children, chronic severe diarrhoea can result in malnutrition, failure to thrive, and significant intestinal fluid losses leading to severe dehydration and even death. Clinical history or physical examination does not allow differentiation of *Cryptosporidia* from other pathogens.

*Cryptosporidia* can migrate into the bile duct and result in inflammation of the biliary epithelium, acalculous cholecystitis, and sclerosing cholangitis. Symptoms include fever, right upper abdominal pain, and elevated alkaline phosphatase. While infection is usually limited to the gastrointestinal tract, pulmonary or disseminated infection can also (rarely) occur in immunocompromised children.

In addition to acute and chronic diarrhoea, *Microsporidia* species have been described in cases of hepatitis, peritonitis, keratoconjunctivitis, myositis, cholangitis, sinusitis, and disseminated CNS disease.

### ***Diagnosis***

At least three stool samples should be submitted for oocyst evaluation by concentration using the sucrose flotation or formalin-ethyl acetate method to concentrate the oocysts. A sample is then stained using a modified Kinyoun acid-fast stain and examined for small (4-6µm in diameter) acid-fast positive oocysts. Enzyme immuno-assays to detect antigens in stool samples are preferred to staining methods because of enhanced sensitivity and specificity.

For diagnosis of *Microsporidia* infection, thin smears of unconcentrated stool-formalin suspension or duodenal aspirates can be stained with modified trichrome stain. Microsporidia spores are stained pink to red by the chemofluorescent agent Calcofluor White, are 1-3µm in size and ovoid, and contain a distinctive equatorial-belt-like stripe. Urine sediment examination by light microscopy can be used to identify microsporidia spores in disseminated disease with *Encephalitozoonidae* and *Trachipleistophora*.

### ***Treatment Recommendations***

Immune reconstitution (an increase in CD4+ T count to >100 cells/mm<sup>3</sup>) resulting from highly active antiretroviral therapy (HAART) frequently results in clearance of *Cryptosporidia*. Effective HAART is the treatment of choice for both of these infections. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided.

There is no consistently effective therapy for cryptosporidiosis, and the duration of treatment in HIV-infected individuals is uncertain. Several agents have demonstrated some efficacy in decreasing the severity of symptoms in children. Nitazoxanide is effective for treatment of paediatric diarrhoea caused by *Cryptosporidia* and *Giardia lamblia*, and is available in a liquid formulation. Other potential alternative treatments include paromomycin and azithromycin.

For treatment of *Microsporidia* infection, albendazole has been reported to decrease diarrhoea, sometimes with eradication of the organism. It is most effective for cases due to *E. intestinalis* and other *Microsporidia* species, but is not active against *E. bienesi*. Fumagillin is an antibiotic derived from the fungus *Aspergillus fumigatus* that has been used to treat *E. bienesi* microsporidiosis diarrhoea and topically to treat microsporidial ocular infections.

## **MYCOBACTERIUM TUBERCULOSIS**

### ***Epidemiology***

Tuberculosis (TB) is one of the leading causes of morbidity and mortality in HIV-infected individuals.<sup>14</sup> The prevalence of HIV infection among patients with TB in Caribbean countries varies from 30% in

Jamaica to 40% in the Bahamas to 52.8% in Trinidad & Tobago.<sup>15</sup> In 1999, the prevalence of TB in HIV-infected individuals living in Haiti was 63.8%.

Data regarding the epidemiology of TB in HIV-infected children in the Caribbean are sparse. In Haiti, where the reported prevalence of TB is reported to be 123 per 100,000 individuals, 38% of orphans with no documentation of BCG vaccine had positive purified protein derivative (PPD) tests (38,202 per 100,000); there were ten active cases.<sup>16</sup> Similarly, there were four paediatric cases of active TB with two reported deaths in an orphanage in Jamaica, with concurrent outbreaks of scabies and varicella.<sup>17</sup> In the Dominican Republic between 1982 and 1986, rates of pulmonary TB were reported to be 46 per 100,000 children. The greatest mortality at that time was due to miliary and meningeal forms of TB and occurred in infants age one year or younger.<sup>18</sup> Seven and one-half percent (7.5%) of HIV-infected children followed in Jamaica have been diagnosed with TB.<sup>19</sup> In addition, TB was the presenting condition in 2.5% of HIV-infected children in Barbados.

Data from international sources suggest an increased risk of TB disease in HIV-infected children. In Jamaica, there was a statistically significant increase in HIV and TB co-infections over a four-year period in children attending the University Hospital of the West Indies.<sup>20</sup> Morbidity and mortality were higher in HIV-infected children who did not receive antiretroviral drugs (ARVs). A study of 204 children in the Dominican Republic with TB showed no difference between HIV-infected and -uninfected children with respect to clinical symptoms or anatomic sites of TB. HIV-infected children were less likely to have a reactive PPD induration of  $\geq 5$ mm and failed treatment significantly more frequently than HIV-uninfected children.<sup>21</sup> Additionally, there were more deaths among HIV-infected children than among HIV-uninfected children, although whether this was attributable to TB could not be determined.

Extrapulmonary and miliary TB are more common in younger children (age four years or younger). Younger children are also more likely to progress more rapidly from infection to active disease than older children and adults, and may often not be recognised as having TB disease because they may have negative skin tests and fewer symptoms of disease.

Congenital TB is rare but has been reported in children born to HIV-infected women with active TB. The true incidence of congenital TB is not known, nor is it known whether this disease is more common in children born to HIV-infected women with active TB as compared with children born to HIV-uninfected women with active TB. Congenital TB can result from haematogenous dissemination of *M. tuberculosis* following maternal mycobacteraemia, rupture of a placental tubercule into the foetal circulation, or ingestion of infected amniotic fluid or maternal blood at delivery. The mother may not have symptoms of TB disease, and subclinical maternal genital TB can also result in an infected neonate.

Children with TB disease are almost always infected by an adult in their daily environment, often a household contact, and their infection represents primary infection rather than the re-activation disease commonly seen in adults.<sup>22</sup> Identification and treatment of the source case is particularly important and all exposed children and other exposed members of the household should be evaluated because other secondary TB cases and latent infections with *M. tuberculosis* are often found. Latent infections should be treated to prevent progression to active disease. HIV counselling and testing should be offered to TB contacts, because co-existing HIV infection, which increases the risk of TB disease, can reduce the sensitivity of the tuberculin test.

The prevalence of multi-drug resistant TB (MDR-TB) in the Caribbean is not known. Drug resistant *M. tuberculosis* is as transmissible as drug susceptible *M. tuberculosis*, and remains drug resistant in a new host. Contacts to drug resistant TB should be treated under the assumption that any newly diagnosed infections are similarly drug resistant.

### ***Clinical Manifestations***

Congenital TB often presents with early symptoms of poor feeding and failure to gain weight during the first few weeks of life; upper respiratory symptoms and progressive hepatosplenomegaly may appear

somewhat later. Fever, progressive pneumonia, and meningitis may occur. Some infants may present more acutely with progressive respiratory distress, apnoea, jaundice, and abdominal distension.

Children with pulmonary TB may have weight loss, fever, and failure to thrive, or they may have few or no symptoms. TB in young children rarely manifests with the typical apical lung infiltrates and cavitations seen in adults with TB. More commonly, pulmonary TB presents as a localised pulmonary infiltrate with associated hilar lymphadenopathy—the primary complex. Multiple lobes are involved in up to 25% of children. Concomitant atelectasis may be seen resulting from hilar adenopathy compressing bronchi or from endobronchial granulomas.

Clinical presentation of TB disease in HIV-infected children is similar to that in HIV-uninfected children. HIV-infected children are more likely to be younger, have failure to thrive, splenomegaly, hepatomegaly, and generalised lymphadenopathy as compared with HIV-uninfected children with TB. Additionally, HIV-infected children have longer hospital stays and greater mortality despite appropriate anti-TB medications.<sup>23</sup> Signs and symptoms may be consistent with acute pneumonia, and radiological evaluation may show non-specific opacities without hilar adenopathy. Older HIV-infected children and adolescents may have clinical presentations more similar to that seen in HIV-infected adults.

Commonly reported sites of extrapulmonary disease in children include lymph nodes, haematogenous (miliary), CNS, bone, kidney, pericardium, peritoneum, and pleura.

### **Diagnosis**

It is essential to have a high index of suspicion for TB disease in HIV-infected children. Diagnosis of TB disease is difficult in children. *M. tuberculosis* can be detected in gastric aspirate samples from approximately 50% of children without HIV infection who have TB disease. Other illnesses with similar symptoms and radiographic abnormalities such as chronic lymphoid interstitial pneumonitis and pulmonary bacterial infections further complicate the diagnosis of TB disease in the HIV-infected child.

Because of the difficulty in obtaining a definitive culture-proven diagnosis of TB disease in children, often the diagnosis of TB disease involves linking the child to an adult with confirmed pulmonary TB together with a positive tuberculin skin test (TST) and an abnormal radiograph or physical examination in the child. However, a negative TST result cannot exclude TB disease in children, as approximately 10% of children without HIV infection but with culture-positive TB disease do not react initially to a TST. HIV infection further decreases TST reactivity.

Because children with HIV infection are considered at high risk for TB, annual Mantoux testing of this population is recommended, beginning at age three to twelve months, using intradermally injected 5TU PPD. Five millimetres (5mm) or more of induration is considered to be a positive (diagnostic) reaction in children and adults with HIV infection. Although the BCG vaccine is routinely given in the majority of Caribbean islands, the Mantoux skin test must still be read without regard to the BCG vaccination status. Children age two years or younger or those who have HIV infection may be more likely to have a negative skin test. Multiple puncture TB skin tests (e.g. tine) are not recommended.

A definitive diagnosis of TB disease requires isolation of *M. tuberculosis* from expectorated sputum; BAL fluid; aspirated gastric fluid (obtained in the early morning after the child fasts overnight); biopsied lung, peripheral lymph node, or other tissue (depending on location of disease); or mycobacterial blood culture. In addition, availability of an isolate allows drug susceptibility testing to be performed.

Three consecutive morning gastric aspirates yield a positive culture of *M. tuberculosis* in up to 70% of infants and 30% to 50% of children with clinical pulmonary TB. Gastric lavage samples, collected on three consecutive mornings, have a higher yield on culture (50%) than a single sample collected by BAL (10%). Nasopharyngeal aspiration and sputum induction are safe and effective in identifying *M. tuberculosis*. The culture yield from other fluids and tissues from children with extrapulmonary TB is less than 50% even with optimal samples.

Antimycobacterial drug susceptibility testing should be performed on the initial *M. tuberculosis* isolate if it is available and on subsequent isolates if treatment failure or relapse is suspected. Prior to obtaining results of susceptibility testing, or if an organism from the child cannot be obtained, the antimycobacterial drug susceptibility of the *M. tuberculosis* isolate from the adult source case can be used to define the likely drug susceptibility of the child's organism and used to design the empiric therapeutic regimen for the child.

### ***Treatment Recommendations***

The principles for treatment of TB in the HIV-infected child are the same as for the HIV-uninfected child. However, optimal therapy has not been defined, and modified treatment durations, schedules, and medications are recommended for specific instances as described in this section.

Because of the high risk of dissemination in children age four years or younger, TB treatment should be begun as soon as the diagnosis of TB is suspected. TB treatment should be initiated four to eight weeks prior to initiating ART in the ARV-naïve child in order to improve adherence and better monitor and reduce potential toxicities of TB treatment. For children already receiving ART who are diagnosed with TB, the child's ARV regimen should be reviewed and altered, if needed, to ensure optimal treatment for both TB and HIV and to minimise potential toxicities and drug-drug interactions.

Directly observed therapy (DOT) is the mainstay of treatment for children and adolescents with TB. It decreases rates of relapse, treatment failures, and drug resistance. For the first two months of treatment, DOT should be given daily (*induction phase*); some experts feel that this can best be achieved by hospitalisation. After this, DOT is usually given two to three times weekly (*continuation phase*). For patients on rifampin (RIF)- or rifabutin-based regimens and who have severe immunosuppression, thrice-weekly regimens are preferred due to concerns related to development of rifamycin resistance by *M. tuberculosis*. However, data on the efficacy of thrice-weekly regimens in children are limited, and healthcare providers may want to continue daily DOT.

Initial empiric treatment of active disease (induction phase) should generally consist of a four-drug regimen (isoniazid (INH), RIF, pyrazinamide (PZA), and either ethambutol (EMB) or streptomycin) to ensure efficacy against a potentially drug resistant organism. Ethionamide may be used as an alternative to EMB in cases of TB meningitis as it has increased CNS penetration. If the organism is found to be susceptible to INH, RIF, and PZA during the two-month period of induction therapy, EMB can be discontinued and induction therapy completed using three drugs. INH and RIF should then be continued daily or intermittently (two to three times weekly) to complete a minimum of nine months of therapy. However, children with severe immunosuppression should receive either daily or thrice-weekly treatment during the continuation phase, because TB treatment regimens with once- or twice-weekly dosing have been associated with an increased rate of acquisition of rifamycin resistance in HIV-infected adults with low CD4+ T cell counts (<100 cells/mm<sup>3</sup>).

The optimum duration of treatment for TB disease in HIV-infected children is controversial, though most experts agree that for HIV-infected children with active pulmonary disease, the minimum recommended duration of antituberculous drug treatment is nine months; for children with extrapulmonary disease involving the bones or joints, CNS, or miliary disease, the minimum recommended duration of treatment is twelve months. These recommendations assume that the organism is susceptible to the medications, that adherence to the medications has been assured, and that the child has had a clinical and microbiologic response to therapy.

### ***Treatment of Drug Resistant TB***

A minimum of three drugs should be given including at least two bactericidal drugs to which the isolate is susceptible. Regimens may include three to six drugs with varying levels of activity.

If the strain is resistant only to INH, INH should be discontinued and the patient treated with nine to twelve months of a RIF- or rifabutin-containing regimen (e.g. RIF, PZA, and EMB; ethionamide or streptomycin could be substituted for EMB if the *M. tuberculosis* isolate is sensitive to these agents).

If the strain is resistant only to RIF, there is an increased risk of relapse and treatment failure. RIF should be discontinued, and a two-month induction phase of INH, PZA, EMB, and streptomycin given, followed by an additional continuation phase of INH, PZA, and EMB to complete a minimum of a twelve-month course of therapy, with the exact length of therapy based on clinical and radiologic improvement. In older adolescents with RIF monoresistant strains, INH, EMB, and a fluoroquinolone such as levofloxacin may be given, with PZA added for the first two months; an injectable agent (e.g. an aminoglycoside such as streptomycin or amikacin) may also be included in the first two to three months for children with severe disease.

When the strain is resistant to both INH and RIF (MDR-TB), therapeutic regimens must be individualised based on the resistance pattern, relative activities of the drugs, extent of disease and any co-morbid conditions. Therapy frequently requires twelve to twenty-four months. Consultation with an expert in the management of paediatric TB is recommended.

### ***Monitoring and Adverse Events***

INH may cause gastric upset during the initial weeks of treatment. Hepatotoxicity is the most common adverse effect and includes subclinical hepatic enzyme elevation and clinical hepatitis that can rarely progress to hepatic failure. When INH is given in a dosage exceeding 10mg/kg in combination with RIF, the incidence of hepatic toxicity may be increased. Other toxicities reported with INH include peripheral neuritis, mild CNS effects, and rare hypersensitivity reactions. Adverse effects typically resolve upon discontinuation of the drug. Pyridoxine is recommended for children and adolescents on meat- and milk-deficient diets and for children with nutritional deficiencies, including all symptomatic HIV-infected children.

RIF is excreted in urine, tears, sweat, and other body fluids and colours them orange. The most common adverse reaction to RIF therapy is gastrointestinal upset. Other reactions include skin rash, hepatitis, and rarely, thrombocytopenia and cholestatic jaundice. RIF induces hepatic cytochrome P450 enzymes and can thus accelerate clearance of drugs metabolised by this pathway, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), potentially resulting in subtherapeutic levels of these agents. As a result, concurrent administration of RIF and single PIs, with the exception of ritonavir (RTV), is not recommended. Concomitant administration of RIF with efavirenz (EFV) is possible in the older child. Regimens that include both RIF and nevirapine (NVP) should be used only when no other options are available, because concomitant administration of these drugs results in a significant decrease in plasma NVP levels.

PZA may cause hepatotoxicity, hyperuricaemia, arthralgias, skin rash, and gastrointestinal intolerance. EMB may cause optic neuritis, with symptoms of blurry vision, central scotomata, and red-green colour blindness, which is usually reversible and is rare at doses of 15mg/kg in children with normal renal function. Children receiving EMB should have monthly monitoring of visual acuity and colour discrimination if possible. Other toxicities include headache, nausea, peripheral neuropathy, rash, and hyperuricaemia.

Unlike children without HIV infection, HIV-infected children on anti-TB medications and ART should have liver enzymes obtained at baseline and monthly for the first few months of therapy. If symptoms of drug toxicity develop, a physical examination and repeat liver enzyme measurement should be performed. Mild elevations in serum transaminases (two to three times upper limit of normal) do not require discontinuation of drugs if other findings are normal.

Adjunctive treatment with corticosteroids in children with TB is indicated for children with TB meningitis, as dexamethasone has been shown to lower mortality and long-term neurologic impairment.

Steroids may also be considered for children with pleural or pericardial effusions, severe miliary disease, and significant endobronchial disease. Appropriate anti-TB therapy must be given concomitantly. Most experts use 1mg to 2mg/kg/day of prednisone or its equivalent for six to eight weeks.

Monthly monitoring of clinical and bacteriologic response to therapy is important. For children with pulmonary TB, chest radiographs should be obtained after two to three months of therapy to evaluate response. Hilar adenopathy may persist for as long as two to three years despite successful anti-TB therapy, and a normal radiograph is not required before discontinuation of therapy. Follow-up radiographs after completion of therapy are not necessary unless clinical symptoms recur.

IRS (an increase in CD4+ T cell count to  $>100$  cells/mm<sup>3</sup>) in patients receiving anti-TB therapy in the setting of HAART has been reported in HIV-infected adults. It is not certain if this occurs in children. New onset of systemic symptoms, especially high fever, expanding CNS lesions, and worsening adenopathy, pulmonary infiltrates, or pleural effusions, have been reported in the setting of HAART up to several months after starting TB therapy. Individuals with mild to moderate symptoms of IRS have been treated symptomatically with nonsteroidal anti-inflammatory drugs (NSAIDs) while continuing anti-TB therapy and HAART. If NSAIDs fail to result in clinical improvement, a short course (e.g. four weeks) of systemic corticosteroid therapy while the child continues to receive HAART can be considered, though data regarding this intervention are lacking.

### ***Infection Control***

In general, children with active TB are usually not infectious, as the concentration of TB bacilli in sputum is usually sparse. This may not apply for children with HIV-TB co-infection. Children with HIV and TB co-infection should be nursed in a room with air at negative pressure. Household family members and close contacts who are visiting may be the adult source for TB and should also be evaluated. Investigations should include a chest radiograph and Mantoux skin test. All children should be reported to public health authorities if TB is *suspected*, enabling the appropriate community investigation and intervention.

## ***MYCOBACTERIUM AVIUM COMPLEX (MAC) DISEASE***

### ***Epidemiology***

*Mycobacterium avium* complex (MAC) is caused primarily by the environmental nontuberculous mycobacteria *M. avium*, *M. intracellulare*, and *M. paratuberculosis*. Respiratory and gastrointestinal colonisation by inhalation or ingestion can subsequently lead to disseminated infection.

Although it has been reported as the second most frequent OI in HIV-infected children in the U.S., its incidence in the Caribbean is uncertain, as it has only been reported in one child in Jamaica.<sup>24</sup> Whether this is due to decreased exposure to the organism or difficulties in diagnosis is unclear.

MAC can present as isolated lymphadenitis in HIV-infected children. Presentation with isolated MAC pulmonary disease is a marker of high risk for dissemination. Disseminated infection with MAC in paediatric HIV infection rarely occurs during the first year of life; its frequency increases with age and declining CD4+ T cell count, and it is a frequent complication of advanced immunologic deterioration in HIV-infected children. In children age two years or younger, disseminated MAC may occur at higher CD4+ T cell counts than it does in older children or adults.

### ***Clinical Manifestations***

Recurrent fever, weight loss or failure to thrive, neutropaenia, night sweats, fatigue, chronic diarrhoea, malabsorption, and persistent or recurrent abdominal pain are the symptoms most commonly associated with disseminated MAC infection in children. Lymphadenopathy, hepatomegaly, and splenomegaly may also be found. Laboratory abnormalities may include anaemia, leukopaenia, and thrombocytopaenia.

### ***Diagnosis***

Procedures used to diagnose MAC in children are the same as those used in HIV-infected adults. Definitive diagnosis is based on isolation of the organism from blood or biopsy specimens from normally sterile sites, such as bone marrow, lymph node, or other tissues. Several mycobacterial blood cultures over time may be required to yield a positive result. Culture is essential to differentiate nontuberculous mycobacteria from *M. tuberculosis* as well as to determine which nontuberculous mycobacteria is the cause of infection and the organism's drug susceptibilities. Identification of MAC in stool or respiratory tract secretions indicates colonisation but not necessarily invasive disease.

### ***Treatment Recommendations***

Combination therapy with a minimum of two drugs is recommended for treatment of MAC infections. Monotherapy with a macrolide results in emergence of high-level drug resistance within weeks.

Initial empiric therapy consists of clarithromycin plus EMB. Azithromycin may be substituted in patients with significant intolerance to clarithromycin or when drug interactions with clarithromycin are a concern. Rifabutin may be added as a third drug to the clarithromycin/EMB regimen, particularly in patients with more severe symptoms or disseminated disease.

Additional drugs can be considered depending on the severity of illness. In a patient with severe disease, if rifabutin cannot be given, ciprofloxacin, levofloxacin, and/or amikacin or streptomycin can be used.

The most effective way to prevent disseminated MAC in HIV-infected children is to preserve immune function through use of effective HAART. Additionally, improved immunologic status is important for control of MAC disease in children with disseminated disease; HAART should therefore be initiated in children with MAC disease who are ARV-naïve.

### ***Monitoring and Adverse Events***

Most patients will show substantial clinical improvement in the first four to six weeks of therapy with decreased fever and increased weight gain. Microbiologic response may take up to twelve weeks of effective therapy and should be monitored by blood cultures every four weeks during initial therapy.

Major toxicities of clarithromycin and azithromycin include nausea, diarrhoea, and abdominal pain. Uncommon toxicities include headache, leukopaenia, altered taste, and elevated transaminases. Clarithromycin can inhibit hepatic metabolism of other drugs cleared by the liver, thus potential drug interactions with concomitantly administered drugs need to be considered.

EMB may cause optic neuritis, with symptoms of blurry vision, central scotomata, and red-green colour blindness, which is usually reversible and is rare at doses of 15mg/kg. Children receiving EMB should have monthly monitoring of visual acuity and colour discrimination if possible. Other toxicities include headache, nausea, peripheral neuropathy, rash, and hyperuricaemia.

Major toxicities of rifabutin include leukopaenia, gastrointestinal upset, polyarthralgias, rash, elevated transaminases, and skin and secretion discoloration (pseudojaundice). Anterior uveitis has been reported in adults and children receiving rifabutin as prophylaxis or as part of a combination regimen for treatment, usually when given at higher doses.

Drug-drug interactions between rifabutin and ARVs can complicate the dosing of rifabutin. If added to the clarithromycin/EMB regimen in a child whose HAART regimen includes RTV, indinavir (IDV), nelfinavir (NFV), amprenavir (APV), or ritonavir-boosted saquinavir (SQV/r), the rifabutin dose must be reduced by 50%. Conversely, the dose of rifabutin must be increased by 50% to 100% if co-administered with EFV.

Adverse effects of quinolones include gastrointestinal upset, diarrhoea, rash, and headache. Cartilage damage has been seen with use of the fluoroquinolone drugs in animals, and theoretically, these drugs could have an effect on growing cartilage in children. Of the quinolone drugs, ciprofloxacin has had the

greatest use in children, appears to be well-tolerated, and has not been associated with arthropathy in clinical practice.

IRS (an increase in CD4+ T cell count to  $>100$  cells/mm<sup>3</sup>) in patients receiving MAC therapy in the setting of HAART has been reported in HIV-infected adults. New onset of systemic symptoms, especially fever or abdominal pain, leukocytosis, and focal lymphadenitis (cervical, thoracic, or abdominal) associated with pre-existing but relatively asymptomatic, often unrecognised, MAC infection has been seen after starting HAART. Thus, before initiation of HAART in HIV-infected children with very low CD4+ T cell counts, consideration should be given for an assessment for MAC and treatment if MAC is identified. Children with moderate symptoms of IRS may be treated symptomatically with NSAIDs or, if unresponsive to NSAIDs, a short course (e.g. four weeks) of systemic corticosteroid therapy while continuing to receive HAART.

### ***Prevention of Recurrence***

In HIV-infected children with MAC disease, following initial therapy, lifetime chronic suppressive maintenance therapy for MAC (secondary prophylaxis) is required; detailed recommendations can be found in the *Chapter VI: Recommendations for Adult and Paediatric Opportunistic Infections Prophylaxis*. The safety of discontinuation of secondary prophylaxis following immunologic recovery with HAART in children has not been studied extensively.

## **SERIOUS AND RECURRENT BACTERIAL INFECTIONS**

### ***Epidemiology***

Serious and recurrent bacterial infections are a major cause of morbidity and mortality in HIV-infected children worldwide. Immunologic defects in both cell-mediated (T cell) and humoral (B cell) immunity, functional asplenia, decrease in neutrophil number and function, and defects in complement components all contribute to the increased susceptibility to bacterial agents in these children. In Jamaica, more than 16% of HIV-infected children presenting with CDC Category C disease and 35% presenting with CDC Category B disease suffered from serious and recurrent bacterial meningitis, pneumonia, or sepsis.<sup>25</sup>

Chronic lung disease such as lymphoid interstitial pneumonitis, often seen in children with HIV infection, may predispose to development of acute pneumonia. Acute pneumonia has been associated with increased risk of long-term mortality in HIV-infected children, although multiple episodes of acute pneumonia likely represent a marker of progressive disease and immunologic dysfunction rather than being causally associated with increased long-term mortality. Serious and recurrent bacterial infections such as pneumonia, meningitis, and sepsis associated with malnutrition were the most common causes of mortality in HIV-infected children in Haiti and the Dominican Republic during the late 1980s and early 1990s.<sup>26</sup>

*Streptococcus pneumoniae* is the most prominent invasive bacterial pathogen in children with HIV infection worldwide, accounting for more than 50% of bacterial blood-stream infections. In the mid-1990s, HIV infection was the single most frequent condition predisposing patients to pneumococcal infection in Trinidad.<sup>27</sup> In Jamaica, children infected with HIV have a markedly increased risk for invasive pneumococcal infection compared with uninfected children and have greater mortality.<sup>28</sup> Approximately 30% of community-acquired sepsis in HIV-infected Jamaican children was due to this organism.

The rate of antibiotic resistance to *S. pneumoniae* varies throughout the Caribbean. In 1997, the prevalence of *S. pneumoniae* susceptibility to penicillin was almost 93% in the West Indies (including both Jamaica and Trinidad).<sup>29</sup> A later study in 1999 of invasive pneumococcal isolates in Jamaican children suggested that penicillin resistance had increased (approximately 86% susceptible) with almost a 20% resistance to co-trimoxazole.<sup>30</sup>

*Haemophilus influenzae* type B (Hib) was reported to be the most common cause of bacterial meningitis in infants in Cuba, in children age five years or younger in the Dominican Republic (13 cases per 100,000), and in Jamaica (39 cases per 100,000) prior to the availability of the Hib vaccine.<sup>31</sup> HIV-infected children are at greater risk of overall invasive Hib disease and of developing bacteraemic pneumonia than are uninfected children. Since 1998, when the Hib vaccine became available in Cuba, a significant decrease in the number of cases of meningitis due to Hib was witnessed there. However, there has also been an increase in the prevalence of mono- and multi-drug resistance in meningitis isolates (including ampicillin, chloramphenicol, TMP-SMX, and tetracycline) from 1990 to 2000.<sup>32</sup>

While the frequency of gram-negative bacteraemia is lower than gram-positive bacteraemia in HIV-infected children, gram-negative bacteraemia is more common in children with advanced HIV disease or immunosuppression or those with central venous catheters. Gram-negative bacteria such as *E. coli* and *Klebsiella pneumoniae* commonly cause urinary tract infections in Jamaican children with HIV infection.<sup>33</sup> However, in children age five years or younger, gram-negative bacteraemia is also seen in children with milder levels of immune suppression.

The presence of a central venous catheter increases the risk of bacterial infections in HIV-infected children, but the incidence is similar to that seen in children with cancer. *S. aureus* is the most commonly isolated pathogen in catheter-associated bacteraemia in HIV-infected children; *P. aeruginosa* is also common. Other organisms associated with catheter-associated bacteraemia include *S. epidermidis*, *Enterococcus*, and *Bacillus cereus*.

### ***Clinical Manifestations***

HIV-infected children with invasive bacterial infections generally have a clinical presentation similar to children without HIV infection. The classical signs, symptoms, and laboratory test abnormalities that usually indicate invasive bacterial infection (fever, elevated white blood cell [WBC] count) are usually present but may be lacking in immunocompromised HIV-infected children. Due to difficulties in obtaining appropriate specimens, such as sputum, from young children, bacterial pneumonia is most often a presumptive diagnosis in a child with fever, pulmonic symptoms, and an abnormal chest radiogram unless there is an accompanying bacteraemia. One-third of HIV-infected children who develop acute pneumonia have recurrent episodes.

### ***Diagnosis***

Attempted isolation of a pathogenic organism from normally sterile sites (blood, CSF, pleural fluid) is strongly recommended. This is particularly important in the face of an increasing incidence of antimicrobial resistance, including penicillin resistant *S. pneumoniae* and community-acquired methicillin resistant *S. aureus*.

The diagnosis of pneumonia is typically made on the basis of clinical (e.g. fever, dyspnoea, tachypnea, cough, rales) and radiographic findings, although it is difficult to differentiate viral from bacterial pneumonia clinically. Culture of blood and pleural fluid, if present, should be done.

In bacteraemic children, a source for the bacteraemia should be sought. In addition to routine chest x-rays, other diagnostic radiological evaluations may become necessary (CT chest, abdomen, ultrasound studies) in HIV-infected children with compromised immune systems in order to identify less apparent foci of infection such as bronchiectasis or internal organ abscesses. In children with central venous catheters, both a peripheral and catheter blood culture should be obtained; if the catheter is removed, the catheter tip should be sent for culture.

### ***Treatment Recommendations***

The local prevalence of resistance to common infectious agents when known (penicillin resistant *S. pneumoniae*, methicillin resistant *S. aureus*), and the recent use of prophylactic or therapeutic antibiotics need to be taken into consideration when initiating empiric therapy. Once the organism is identified,

antibiotic susceptibility testing should be performed and therapy commenced based on the results of susceptibility testing.

HIV-infected children whose immune systems are not seriously compromised (CDC Immune Class I) and who are not neutropaenic can be expected to respond like HIV-uninfected children and should be treated with the usual antimicrobial agents recommended for the most likely bacterial organisms. For example, for HIV-infected children presenting with suspected bacteraemia, bacterial pneumonia, or meningitis, empiric therapy with an extended-spectrum cephalosporin such as ceftriaxone, cefotaxime, or cefuroxime would be reasonable until culture results are available.

Initial empiric therapy of HIV-infected children with suspected catheter sepsis should include coverage for both gram-positive and enteric gram-negative organisms, such as ceftazidime, which has anti-*Pseudomonas* activity, and vancomycin to cover methicillin resistant *S. aureus*. Severely immune compromised HIV-infected children presenting with invasive or recurrent bacterial infections may require expanded empiric antimicrobial treatment covering a broad range of resistant organisms (similar to that chosen for suspected catheter sepsis) pending results of diagnostic evaluations and cultures.

HIV-infected children age five years or younger should receive Hib. New conjugate pneumococcal vaccines with a serotype composition relevant to the Caribbean should be given as they become available. Influenza vaccine should also be given yearly.

## **SYPHILIS**

### ***Epidemiology***

*T. pallidum* can be transmitted from mother to child at any stage of pregnancy or during delivery. Untreated or inadequately treated primary and secondary syphilis during pregnancy leads to congenital infection in 60% to 100% of infants. Treatment of the mother for syphilis thirty days or more prior to delivery is required for effective *in utero* treatment.

In Jamaica, the syphilis seroreactivity rate among pregnant women declined from 17% to 2% between 1990 and 2001. During that same time period, the prevalence of primary and secondary syphilis went from 90 cases per 100,000 in 1987 to under 10 cases per 100,000 in 2001. During 2002-2003, 4% of 84 HIV-infected pregnant women in Kingston, Jamaica, had reactive VDRL.<sup>34</sup>

Cases of congenital syphilis in Jamaica have concomitantly decreased from sixty-eight to twenty-one cases between 1994 and 2001.<sup>35</sup> In Trinidad during 1985 to 1988, the annual average incidence of congenital syphilis was 115 per 100,000 live births with a doubling of the incidence in the latter two years of the study.<sup>36</sup> In Haiti from 1985 to 1999, rates of congenital syphilis were 550 per 100,000 live births. This very high rate decreased by 75% to 137 per 100,000 live births after decentralisation of their prenatal screening program.<sup>37</sup> There has been no published data relating the incidence of HIV co-infection and congenital syphilis in the Caribbean.

### ***Clinical Manifestations***

Untreated early syphilis during pregnancy may lead to spontaneous abortion, stillbirth, hydrops fetalis, preterm delivery, and perinatal death in up to 40% of pregnancies. At birth, approximately 60% of infants with congenital syphilis are asymptomatic. If untreated, symptoms may occur within three weeks to six months after birth, and may include hepatosplenomegaly, jaundice, mucocutaneous lesions, skin rash, nasal discharge, pseudoparalysis of an extremity, anaemia, thrombocytopenia, and osteochondritis.

Late manifestations of congenital syphilis (after age two years) involve the CNS, bones, teeth, eyes, and skin. Manifestations include mental retardation, interstitial keratitis, eighth cranial nerve deafness, anterior bowing of the skins, frontal bossing, mulberry molars, Hutchinson teeth, saddle nose, rhaades, and Clutton joints.

HIV-infected children, adolescents, and adults with acquired early syphilis may be at increased risk of neurologic complications and uveitis and have higher rates of treatment failure.

### **Diagnosis**

The diagnosis of neonatal congenital syphilis depends on a combination of results from physical, radiologic, serologic, and direct microscopic examinations. All infants born to women with reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal test such as the VDRL slide test, rapid plasma reagin (RPR), and the automated reagin test. Testing should be performed on neonatal serum due to the potential for maternal blood contamination of the umbilical cord blood specimen. It is not necessary to perform specific treponemal tests, such as the fluorescent treponemal antibody absorption (FTA-ABS) test and *T. pallidum* particle agglutination (TP-PA) test, for evaluation of congenital syphilis in the neonate.

Darkfield microscopic examination or direct fluorescent antibody staining of lesions or body fluids should be performed, although false-negative results are common. Definitive diagnosis of congenital syphilis can be made if *T. pallidum* is detected in umbilical cord, placenta, nasal discharge, or skin lesion material. Pathologic examination of the placenta and umbilical cord with specific fluorescent antitreponemal antibody staining, if available, is recommended.

Evaluation of suspected cases of congenital syphilis should include a physical examination, complete blood count, differential and platelet count, and CSF analysis for VDRL, cell count, and protein. HIV-infected infants may have increased cell counts and protein concentrations even in the absence of neurosyphilis. Other tests should be performed as clinically indicated, such as long-bone radiographs, chest radiograph, liver-function tests, cranial ultrasound, ophthalmologic examination, and auditory brainstem response.

A presumptive case of syphilis is defined as an infant born to a mother with untreated or inadequately treated syphilis at delivery, regardless of findings in the infant; or as any infant who has a reactive treponemal test result and clinical signs or symptoms of congenital syphilis on physical exam or an abnormal CSF finding without other cause or positive CSF VDRL.

For diagnosis of acquired syphilis, a reactive nontreponemal test must be confirmed by a specific treponemal test such as FTA-ABS or TP-PA. These tests will remain positive for life, even with successful treatment. The prozone phenomenon (a weakly reactive or falsely negative) reaction may occur more frequently in HIV-infected individuals. Treponemal antibody titres do not correlate with disease activity and should not be used to monitor treatment response. CSF evaluation should be performed in HIV-infected adolescents with acquired syphilis who have neurologic or ocular symptoms or signs (although some clinicians recommend a CSF examination for all HIV-infected patients).

### **Treatment Recommendations**

Infants should be treated if mothers have untreated or inadequately treated syphilis (including treatment with erythromycin or any other nonpenicillin regimen) or have no documentation of having received treatment, received treatment for four weeks or less prior to delivery, been treated with penicillin but titres did not decrease by four-fold, or have a four-fold or greater increase in nontreponemal antibody titre suggesting relapse or re-infection.

Infants should be treated with aqueous crystalline penicillin G for a total of ten days regardless of maternal history if: 1) there is an abnormal examination consistent with congenital syphilis; 2) positive darkfield or fluorescent antibody test of body fluid(s); or 3) serum quantitative nontreponemal serologic titre that is the same or four-fold greater than the maternal titre. An alternative to aqueous penicillin G is procaine penicillin G intramuscularly for ten days. However, aqueous penicillin G is preferred because of its higher penetration into the CSF.

Asymptomatic infants born to mothers who have had adequate treatment, response to therapy, and normal physical examination and CSF findings, but who have a serum quantitative nontreponemal serologic titre

that is the same or four-fold higher than maternal titre, may be treated with a single dose of benzathine penicillin G intramuscularly, with careful clinical and serologic follow-up. However, some experts would treat such infants with the standard ten days of aqueous penicillin because physical examination and laboratory test results cannot definitively exclude congenital syphilis in all cases.

Acquired syphilis is treated with a single dose of benzathine penicillin G intramuscularly for early stage disease (primary, secondary, early latent disease). For late latent disease, benzathine penicillin G should be given intramuscularly once weekly for three doses. Alternative therapies such as doxycycline, ceftriaxone, or azithromycin have not been evaluated in HIV-infected patients and should not be used as first-line therapy. Neurosyphilis should be treated with aqueous penicillin G intravenously for ten to fourteen days.

### ***Monitoring and Adverse Events***

Infants with treated congenital syphilis should be examined at age one, two, three, six, and twelve months, with serologic nontreponemal tests performed at three, six, and twelve months after conclusion of treatment or until results become nonreactive. If the initial CSF examination was abnormal, repeat lumbar puncture should be done every six months until results are normal. Nontreponemal antibody titres should decline by age three months and be nonreactive by age six months if the infant was adequately treated or not infected (e.g. passive antibody transfer from mother). Children with increasing titres or persistently positive titres (even if low levels) at age six to twelve months should be evaluated and considered for retreatment. Children with congenital syphilis who are also HIV-infected may take longer to become nonreactive and may require retreatment.

Children and adolescents with acquired syphilis should have clinical and serologic response monitored at three, six, nine, twelve, and twenty-four months after therapy. Nontreponemal test titres should decline by at least four-fold by six to twelve months after successful therapy. If the initial CSF examination was abnormal, repeat lumbar puncture should be done at three and six months after therapy and then every six months until results are normal and the VDRL is negative.

## **CANDIDA INFECTIONS**

### ***Epidemiology***

The most common fungal infections in HIV-infected children are due to *Candida* species. Oral thrush and diaper dermatitis occur in 50% to 85% of HIV-infected children. *Candida albicans* is the most common cause of mucosal and oesophageal candidiasis.

Oropharyngeal candidiasis is seen in 37% of HIV-infected children in Barbados, 13% of those in Jamaica, and there was also a predominant finding in Dominican children.<sup>38</sup> *Candida* oesophagitis is reported as the AIDS-defining condition in approximately 2% of Jamaican children presenting with CDC Category C disease.<sup>39</sup>

Disseminated candidiasis is infrequent in HIV-infected children, but *Candida* may disseminate from the oesophagus particularly when co-infection with herpes simplex virus (HSV) or CMV is present. Fungaemia occurs in up to 12% of HIV-infected children with chronically indwelling central venous catheters for total parental nutrition or intravenous antibiotics. Approximately 50% of reported cases of fungaemia in HIV-infected children are caused by non-*albicans* *Candida* species including *C. tropicalis*, *C. pseudotropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei*, and *C. dubliniensis*. A significant number of children who develop fungaemia have received systemically absorbed oral antifungal azole compounds (ketoconazole or fluconazole) for control of oral and oesophageal candidiasis.

Common complications of disseminated candidiasis include endophthalmitis, hepatosplenic and renal candidiasis, and osteomyelitis. Early detection and treatment of candidaemia may decrease mortality.

### ***Clinical Manifestations***

Clinical manifestations of oropharyngeal candidiasis are variable and include pseudomembranous (*thrush*), erythematous (*atrophic*), hyperplastic (*hypertrophic*), and angular cheilitis. Thrush is the most classic form of oral candidiasis, commonly appearing as creamy white curdlike patches with inflamed underlying mucosa that is exposed after removal of the exudate. It can be found on the oropharyngeal mucosa, palate, and tonsils. Erythematous oropharyngeal candidiasis consists of flat erythematous lesions on the mucosal surface. Hyperplastic candidiasis is made up of raised white plaques appearing on the lower surface of the tongue, palate, and buccal mucosa and cannot be removed. Angular cheilitis occurs as red, fissured lesions in the corners of the mouth.

Oesophageal candidiasis can present with odynophagia, dysphagia, or retrosternal pain, which can be severe enough to cause dehydration and weight loss in children. Although common, evidence of oropharyngeal candidiasis may be absent in children with oesophageal candidiasis. Unlike adults, a significant number of children may present with nausea and vomiting.

New onset fever in an HIV-infected child with advanced disease and a central venous catheter is the most common clinical manifestation of candidaemia. Renal candidiasis may present with candiduria and ultrasonographically demonstrate renal parenchymal lesions without symptoms related to renal disease. Systemic fungaemia may lead to endogenous endophthalmitis, and ocular examination by an ophthalmologist may be warranted in children with candidaemia.

### ***Diagnosis***

Diagnosis of oral candidiasis can be made by a KOH preparation and culture with microscopic demonstration of budding yeast cells in wet mounts or biopsy specimens. For recurrent or refractory oropharyngeal candidiasis, cultures with *in vitro* susceptibility testing may be used to guide antifungal treatment.

Oesophageal candidiasis has a classic cobblestoning appearance on barium swallow. With persistent cases, unresponsive to usually effective therapy, one must consider HSV, CMV, MAC, and azole-resistant *Candida* species. Diagnosis of candidaemia is best made with blood cultures. When fungaemia is present, retinal exam for endophthalmitis, abdominal CT or ultrasound for hepatic or renal involvement, and bone scans if osteomyelitis is clinically suspected may be appropriate.

### ***Treatment Recommendations***

Oropharyngeal candidiasis can be treated with fluconazole, clotrimazole troches, nystatin, or amphotericin B suspension. Systemic therapy with ketoconazole or itraconazole is also effective for initial treatment of oropharyngeal candidiasis. Fluconazole is available through National AIDS Coordinators free of cost to all countries with an HIV seroprevalence of more than 1%.

Oesophageal disease should be treated systemically, and treatment with fluconazole or itraconazole should be begun empirically in HIV-infected children with oropharyngeal candidiasis and oesophageal symptoms. In most patients, symptoms should resolve within days of the start of effective therapy. Itraconazole solution or low-dose intravenous amphotericin B may be used for patients with fluconazole-refractory infections. Intravenous caspofungin, an echinocandin inhibitor of fungal (1,3)-beta-D-glucan synthetase inhibitor, has been shown to be effective and comparable to amphotericin B and fluconazole for treatment of oesophageal *Candida* infections and comparable to amphotericin B for treatment of candidaemia in adults.

Central venous catheter candidaemia infection should be treated with intravenous amphotericin B. Duration of therapy in treatment of fungaemia should be determined by presence of deep tissue foci, patient clinical response, and presence of neutropaenia. Lipid formulations may be used in patients who do not tolerate conventional amphotericin B or have severe renal disease. Patients at high risk for morbidity and mortality should be treated for at least two to three weeks after the last positive blood culture and until all signs and symptoms of infection have resolved. Flucytosine has been used in combination with amphotericin B in some patients with CNS invasive candidiasis.

Fluconazole has been used as an alternative to amphotericin B for treatment of invasive disease in stable patients, such as those with uncomplicated candidaemia who have not recently received azole therapy. However, fluconazole should not be initiated in the treatment of fungaemia without knowing the speciation, because species such as *C. krusei* and *C. glabrata* are resistant to fluconazole.

### ***Monitoring and Adverse Events***

The most frequent adverse effects of the azoles drugs are gastrointestinal, including nausea and vomiting, most often reported with ketoconazole (10% to 40% of patients) and less commonly with the other azoles (<5%). Skin rash and pruritus may be seen with all drugs; rare cases of Stevens-Johnson syndrome have been reported with fluconazole therapy. All drugs are associated with asymptomatic increases in transaminases, but rare cases of fatal hepatitis have been reported. Haematologic abnormalities have also been reported, including haemolytic anaemia with ketoconazole, and thrombocytopenia and leukopenia with itraconazole. Ketoconazole has been associated with endocrinologic abnormalities related to steroid metabolism, including adrenal insufficiency and gynecomastia. Fluconazole has been associated with alopecia in scalp and pubic area.

## ***CRYPTOCOCCOSIS***

### ***Epidemiology***

Cryptococcosis is a fungal infection that is inhaled as spores into the lungs and spreads to the meninges and viscera in HIV-infected hosts. It is primarily found in pigeon droppings. Cryptococcal infections occur much less frequently in HIV-infected children than adults. Approximately 1% of children in Jamaica have become infected.<sup>40</sup>

### ***Clinical Manifestations***

Meningoencephalitis is the most common initial manifestation of cryptococcosis, evolving over days to weeks with fever, headache, and altered mental status. It can also present acutely, with nuchal rigidity, seizures, and/or focal neurologic signs. CNS mass lesions (*cryptococcomas*) seen in adults have not been reported in children.

Pulmonary cryptococcus without dissemination is unusual in children but may present as unexplained recurrent fever, cough with scant sputum, intrathoracic lymphadenopathy, and focal or diffuse pulmonary infiltrates. It may be asymptomatic with pulmonary nodules found on routine chest radiograph.

The skin may be secondarily involved in disseminated cryptococcosis. Lesions may be small, translucent, umbilicated papules (indistinguishable from molluscum contagiosum), nodules, ulcers, or infiltrated plaques resembling cellulitis.

### ***Diagnosis***

For diagnosis of suspected CNS disease, microscopic examination of CSF on India ink-stained wet mounts should be performed. Cryptococcal antigen can be detected in CSF, serum, or BAL fluid by latex agglutination test. However, CSF antigen detection may be negative in culture-positive cryptococcal meningitis; high titres of antigen (prozone effect), low levels of antigen, or non-encapsulated strains may contribute to this effect.

In HIV-infected children with CNS disease, the opening pressure is usually elevated and may be the only abnormal finding. Head CT scans are usually nonspecific but may show signs of increased intracranial pressure, hydrocephalus, or focal lesions, especially in the basal ganglia.

Fungal cultures from CSF, sputum, and blood may identify the organism. Diffuse pulmonary disease can be diagnosed via BAL and direct examination of India ink-stained specimens, culture, and antigen detection. Focal pulmonary and skin lesions may require biopsy with culture and staining.

### ***Treatment Recommendations***

Without treatment, cryptococcosis is invariably fatal. Recommendation for the use of combination therapy for severe cryptococcosis and cryptococcal meningitis are based on data from adult studies.

For children with severe disease that is isolated to the lungs, amphotericin B induction therapy, usually combined with an initial two weeks of flucytosine, is recommended until symptoms are controlled. Following treatment of acute pulmonary disease, maintenance therapy with fluconazole or itraconazole is recommended.

For meningeal and extrameningeal cryptococcosis, initial therapy with the combination of amphotericin B plus flucytosine, for a minimum of two weeks (*induction therapy*), is recommended. If flucytosine cannot be used, amphotericin B alone can be given. Lipid formulations of amphotericin B have been used for treatment of cryptococcal meningitis in adults, and may be particularly useful in patients with impaired renal function, although the optimal dose in children has not been determined.

Fluconazole plus flucytosine has been shown to be superior to fluconazole alone and provides an alternative option to amphotericin B for acute therapy of invasive disease, but there are little data on this combination in children.

After successful two-week acute induction therapy, amphotericin B and flucytosine can be discontinued in stable patients, and *consolidation therapy* with fluconazole given for a minimum of eight weeks or until CSF cultures are stable should be commenced. Following induction and consolidation therapy, maintenance suppressive therapy with lower-dose fluconazole should be instituted.

If fluconazole cannot be given, itraconazole is an alternative for consolidation, but may be less active than fluconazole.

Oral acetazolamide should not be used for reduction of elevated intracranial pressure in cryptococcal meningitis; it has been associated with an excess of severe acidosis, hypokalaemia, and other adverse effects. Recommendations for the management of elevated intracranial pressure are the same as for adults.

### ***Monitoring and Adverse Events***

Cryptococcal antigen titres in CSF can be helpful in evaluating response to therapy or ongoing relapse; however, changes in serum antigen titres do not correlate with clinical response. A rise in CSF antigen titre of >1:8 during suppressive therapy is associated with treatment failure or pending relapse.

Amphotericin B is nephrotoxic. Permanent nephrotoxicity is related to cumulative doses. Intravenous hydration is recommended prior to the amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting may occur, although they are less frequent in children than adults. Hepatic toxicity, thrombophlebitis, and anaemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) may also occur. Liposomal preparations may cause acute, infusion-related reactions in about 20% of patients, including chest pain, dyspnoea, and hypoxia; severe abdomen, flank, or leg pain; and/or flushing and urticarial. Premedication with diphenhydramine can reduce the incidence of these reactions.

Flucytosine has the potential for considerable toxicity especially affecting the bone marrow (anaemia, leukopaenia, thrombocytopaenia), liver, gastrointestinal tract, kidney, and skin. Levels should be monitored and doses adjusted to keep the level between 40 to 60µg/mL. The drug should be avoided in children with severe renal impairment.

Fluconazole and the other azoles have relatively low rates of toxicity, but have significant drug interactions that can limit their use. Because of their ability to inhibit the cytochrome P-450-dependent hepatic enzymes, the potential for drug interactions, particularly with ARVs, should be carefully evaluated prior to initiation of therapy. Skin rash and pruritis may be seen with all azole drugs, and rare cases of Stevens-Johnson syndrome have been reported with fluconazole. Asymptomatic increases in

transaminases can be seen and less frequently, hepatitis; rare cases of fatal hepatitis have been reported. Thrombocytopaenia and leukopaenia have been reported with itraconazole.

### ***Prevention of Recurrence***

Prevention of relapse after successful treatment requires lifelong suppressive treatment; details on secondary prophylaxis (maintenance therapy) are provided in *Chapter VI.: Recommendations for Adult and Paediatric Opportunistic Infections Prophylaxis*. Safety of discontinuation of secondary prophylaxis following immune reconstitution with HAART in children has not been studied extensively.

## ***HISTOPLASMOSIS***

### ***Epidemiology***

*Histoplasma capsulatum* is endemic in the Caribbean, living in the soil in bird droppings and bat guano. The incidence of disseminated histoplasmosis in HIV-infected paediatric patients in the Caribbean is unknown. Only one case of disseminated histoplasmosis in an adolescent from Jamaica has been described.<sup>41</sup>

### ***Clinical Manifestations***

The most common presenting symptom in HIV-infected children and adults with disseminated histoplasmosis is prolonged fever. Children predominantly present with malaise and weight loss together with nonproductive cough. Additionally, interstitial pneumonitis as seen in adults is rarely observed in children, but a primary pulmonary focus frequently leads to widespread dissemination in HIV-infected children.

The most frequent physical finding is hepatosplenomegaly. Coetaneous lesions that are erythematous and nodular may occur. CNS involvement with meningitis and focal brain lesions is common in HIV-infected adults and may be due to reactivated infection in the setting of very low CD4+ T cell numbers. Anaemia and thrombocytopaenia are the most common haematologic abnormalities found, although pancytopaenia has been reported. Elevated liver transaminases also occur.

### ***Diagnosis***

Culture of the organism is the definitive method of diagnosis but may require up to six weeks to grow. Detection of *H. capsulatum* polysaccharide antigen by enzyme-linked immuno-assay (EIA), in urine, BAL or CSF, and/or serum is a rapid, sensitive, and specific method for diagnosis; it can be detected prior to culture positivity and, in acute histoplasmosis, is positive prior to antibody detection. EIA sensitivity is greatest in patients with disseminated disease or acute pulmonary infection.

Diagnosis of CNS disease is difficult, particularly if the patient has isolated meningitis without disseminated disease. The highest sensitivity is achieved by testing CSF for *Histoplasma* antigen and antibody as well as culture.

### ***Treatment Recommendations***

Disseminated histoplasmosis is uniformly fatal without antifungal treatment. In HIV-infected children with disseminated histoplasmosis, who require hospitalisation, or who are immunocompromised, amphotericin B is recommended for four to six weeks, followed by itraconazole chronic suppressive therapy. Some experts limit amphotericin B therapy to two to three weeks, followed by three to six months of consolidation therapy with itraconazole after the patient is clinically stabilised and afebrile. For children with confirmed *H. capsulatum* meningitis, amphotericin B therapy should be continued for twelve to sixteen weeks, followed by chronic suppressive therapy (secondary prophylaxis) with itraconazole. Liposomal amphotericin B is an alternative for patients who cannot tolerate conventional amphotericin, and in one randomised trial, was associated with improved treatment response and survival and less toxicity compared to conventional amphotericin B induction therapy.

Mild disseminated histoplasmosis has been effectively treated by itraconazole given for three to twelve months in a small number of non-immunocompromised children without HIV infection. High-dose fluconazole is an alternative for patients with mild histoplasmosis who cannot take itraconazole, but is less effective and the organism may develop drug resistance.

### ***Monitoring and Adverse Events***

Amphotericin B is nephrotoxic. Permanent nephrotoxicity is related to cumulative dose. Intravenous hydration is recommended prior to the amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting may occur, although they are less frequent in children than adults. Hepatic toxicity, thrombophlebitis, and anaemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) may also occur. Liposomal preparations may cause acute, infusion-related reactions in about 20% of patients including chest pain, dyspnoea, and hypoxia; severe abdomen, flank, or leg pain; and/or flushing and urticarial. Premedication with diphenhydramine can reduce the incidence of these reactions.

### ***Prevention of Recurrence***

After successful treatment of acute disease, itraconazole chronic suppressive therapy (secondary prophylaxis) should be instituted. Prevention of relapse after successful treatment requires lifelong suppressive treatment; details on secondary prophylaxis (maintenance therapy) are provided in *Chapter VI.: Recommendations for Adult and Paediatric Opportunistic Infections Prophylaxis*.

## **COCCIDIOIDOMYCOSIS**

### ***Epidemiology***

Coccidioidomycosis is caused by *Coccidioides immitis*. There are no published reports of coccidioidomycosis in children in Caribbean nations.

Primary infection of the newborn occurs rarely. However, infection of the genital tract of the mother can result in placental involvement, coccidioidal endometritis, and aspiration of infected amniotic fluid by the foetus. Both *in utero* and perinatal transmission of *C. immitis* have been reported.

### ***Clinical Manifestations***

Fever and dyspnea are common presenting symptoms in children, along with chills, weight loss, lymphadenopathy, chest pain, and headache.

With pulmonary disease, chest radiographs exhibit bilateral, diffuse reticulonodular pulmonary infiltrates. Some patients may develop persistent pulmonary nodules or thin-walled cavities. Diffuse pneumonia due to *C. immitis* is usually accompanied by fungaemia, and patients should be evaluated for systemic disease and extrapulmonary lesions (e.g. meningitis).

Disseminated disease with diffuse erythematous maculopapular rash, erythema multiforme, erythema nodosum, and/or arthralgias may occur. Infection in bones and joints as well as CNS can also occur.

### ***Diagnosis***

Diagnosis can be made by direct examination and culture of respiratory secretions, CSF, or by biopsy of suspicious pulmonary or coetaneous lesions to reveal characteristic double-contoured spherules with endospores and without budding. Blood cultures may be positive less than 15% of the time in HIV-associated coccidioidomycosis.

IgM antibody, detected by latex agglutination, enzyme immuno-assay, immunodiffusion, or tube precipitin, appears early and is an indication of acute infection. IgG antibody gradually appears over the first few months after primary infection and does not disappear in the presence of disseminated disease. Titres of >1:16 are associated with disseminated disease (except in cases of isolated meningitis). Serological tests such as complement fixation, tube precipitation, and immunodiffusion assays may have reduced diagnostic utility in severely immunosuppressed HIV-infected patients.

### ***Treatment Recommendations***

There is little experience treating coccidioidomycosis in HIV-infected children, and recommendations are generally based on experience with adults.

Based on data from HIV-infected adults, for treatment of diffuse pulmonary or disseminated disease, induction therapy with amphotericin B is recommended until clinical improvement is seen. Following acute therapy, chronic suppressive therapy with fluconazole or itraconazole is recommended.

Treatment of disseminated nonmeningitic infection that is stable may include fluconazole or itraconazole. CNS infections including meningitis should be treated with high-dose fluconazole since unlike amphotericin B, it crosses the blood brain barrier well. For CNS infections unresponsive to fluconazole, intravenous amphotericin B is used and augmented by intrathecal amphotericin B. Consultation with a specialist is recommended when treating children with meningeal disease.

### ***Monitoring and Adverse Events***

The most frequent adverse effects of fluconazole are gastrointestinal, including nausea and vomiting. Skin rash and pruritis may be seen and rare cases of Stevens-Johnson syndrome have been reported with fluconazole. Asymptomatic increases, and less frequently, hepatitis, in transaminases can be seen in 1% to 13% of patients receiving azole drugs; rare cases of fatal hepatitis have been reported.

Surgical debridement or excision of localised, persistent, progressive, or resistant lesions in bone and lung may be helpful. Lung cavities with recurrent bleeding and those >6cm in diameter are at greater risk of rupture and require surgery.

### ***Prevention of Recurrence***

As with other disseminated fungal infections, continued chronic suppressive therapy with fluconazole or itraconazole is recommended following completion of initial therapy; details on secondary prophylaxis (maintenance therapy) are provided in *Chapter VI.: Recommendations for Adult and Paediatric Opportunistic Infections Prophylaxis*. The safety of discontinuation of secondary prophylaxis following immune reconstitution with HAART in children has not been studied extensively.

## ***CYTOMEGALOVIRUS (CMV)***

### ***Epidemiology***

Infection with CMV is common and usually unapparent; acquisition of CMV may occur during infancy, early childhood, or adolescence. Transmission can occur from an infected woman to her offspring; horizontally by contact with virus-containing saliva, urine, or sexual fluid; or via transfusion of infected blood or transplantation of infected organs.

Congenital (*in utero*) CMV infection occurs most commonly in infants born to women with primary CMV infection during pregnancy. CMV can also be transmitted during the intrapartum or postpartum periods from mother to infant. Up to 57% of infants whose mothers shed CMV at or around the time of delivery become infected with CMV, and up to 53% of children who are breastfed with milk that contains the infectious virus can become CMV-infected. However, symptomatic CMV disease in infants is much less common when CMV is acquired intrapartum or through breastfeeding.

A seroprevalence study in Jamaican pregnant women from 1986 showed an overall prevalence rate of CMV antibodies of 97%.<sup>42</sup> The prevalence of CMV infection among HIV-infected pregnant women in the Caribbean is unknown.

The rate of CMV antibody acquisition was 56% in Jamaican preschool-age children.<sup>43</sup> It is unknown whether antibody acquisition differs by HIV-infection status. In HIV-infected children in Barbados, 2.5% of infected children had CMV disease as their presenting clinical condition, while CMV represented 2% of CDC Category C disease in Jamaican children.<sup>44</sup>

### ***Clinical Manifestations***

Approximately 10% of infants with *in utero* CMV infection are symptomatic at birth with congenital CMV syndrome (CMV inclusion disease); mortality of children with symptomatic disease is as high as 30%. Newborns with symptomatic congenital CMV infection are generally small for gestational age, and may have purpura/petechiae, jaundice, hepatosplenomegaly, chorioretinitis, microcephaly, intracranial calcifications, and hearing impairment. Ninety percent (90%) of infants with symptomatic disease at birth who survive have late complications, including significant hearing loss, mental retardation, chorioretinitis, optic atrophy, seizures, or learning disabilities.

Although the majority of children with *in utero* CMV infection do not have symptoms at birth, 10% to 15% are at risk of developing later developmental abnormalities, sensorineural hearing loss, chorioretinitis, or neurologic defects.

HIV-infected children with CMV co-infection may have accelerated progression of HIV disease compared to those without CMV infection. CMV retinitis is the most frequent severe manifestation of CMV disease in HIV-infected children. CMV retinitis in young HIV-infected children is frequently asymptomatic. Older children with CMV retinitis present similarly to adults with floaters, loss of peripheral vision, or reduction in central vision.

HIV-infected children with CD4+ T cell counts of  $<100$  cells/mm<sup>3</sup> are more likely to develop CMV retinitis than those with higher CD4+ T cell counts, but CD4+ T cell count is less predictive of risk for CMV disease in young infants, and systemic and localised CMV disease can also occur in HIV-infected infants with higher age-adjusted CD4+ T cell counts.

End-organ CMV disease may occur in the lung, liver, gastrointestinal tract, pancreas, kidney, sinuses, and CNS. In children with extra-ocular CMV disease, predominantly nonspecific symptoms such as fever, poor weight gain, and loss of developmental milestones may occur. Gastrointestinal manifestations in HIV-infected children include CMV colitis (the most common GI manifestation), oral and oesophageal ulcers, hepatic involvement, ascending cholangiopathy, and gastritis.

The role of CMV in pulmonary disease in HIV-infected children is difficult to assess as it is often isolated with other organisms, such as *P. jiroveci*. Histologic evidence of CMV disease is needed to determine if active disease is present. CMV pneumonia is an interstitial process with gradual onset of shortness of breath and dry, nonproductive cough.

CNS manifestations of CMV include subacute encephalopathy, myelitis, and polyradiculopathy (primarily seen in adults but rarely reported in children). CSF findings are nonspecific, and may show a polymorphonuclear predominance, elevated protein, and low glucose.

### ***Diagnosis***

CMV *infection* versus *disease* may be difficult to differentiate in HIV-infected children. In most Caribbean countries, diagnosis in paediatric patients is primarily clinical and presumed when other aetiologies have been ruled out. Due to transplacental transfer of antibody from mother to child, a positive CMV antibody assay in an infant age twelve months or younger is indicative of maternal infection but not necessarily infection of the infant. In an infant age twelve months or older, a positive CMV antibody assay indicates prior infection with CMV but not necessarily active disease. At any age, a positive CMV culture is indicative of infection, but again not necessarily of disease.

Oesophagitis due to CMV can be diagnosed based on characteristic shallow ulcerations at the distal oesophagitis with histopathologic changes. Histopathology demonstrates characteristic “owl’s eye” intranuclear and smaller intracytoplasmic inclusion bodies in biopsy specimens. Diagnosis of CMV retinitis is based on clinical appearance, with white and yellow retinal infiltrates and associated retinal haemorrhages.

### ***Treatment Recommendations***

Most drugs for the treatment of CMV are not currently accessible or available in the Caribbean. However, in countries where treatment is available, intravenous ganciclovir for two to three weeks should be used in the treatment of newborns with severe or life- or sight-threatening congenital CMV disease.

The drug of choice for initial treatment of disseminated CMV disease, including CMV retinitis, in HIV-infected children is intravenous ganciclovir followed by lifelong maintenance therapy. With long-term therapy, the emergence of ganciclovir resistant CMV strains has occurred.

Foscarnet, given for fourteen to twenty-one days followed by lifelong maintenance therapy, is used as an alternative in ganciclovir resistant CMV infections in HIV-infected children. Combination therapy with ganciclovir and foscarnet may be helpful in patients failing monotherapy and may be used as initial therapy in children with sight-threatening disease. Valganciclovir, a prodrug of ganciclovir, is one of the first-line treatments for HIV-infected adults with CMV retinitis.

Prior to the availability of valganciclovir, oral ganciclovir (in combination with an intraocular ganciclovir implant) had been used for maintenance treatment of CMV retinitis in older children. In children old enough to receive adult dosage, valganciclovir would be the preferred drug over oral ganciclovir.

Intravitreal injections of ganciclovir, foscarnet, or cidofovir have been used for control of retinitis, but require biweekly intraocular injections. Data are limited in children, and biweekly injections are impractical for use in most children. Implantation of an intravitreal ganciclovir medication release device in the posterior chamber of the eye has also been used in HIV-infected adults and adolescents. Intraocular implants should not be used in children age three years or younger due to the small size of young children's eyes.

### ***Monitoring and Adverse Events***

Complete blood counts, including platelet counts and liver enzyme counts, should be done twice weekly to monitor for drug-induced effects. The major side effect of ganciclovir is myelosuppression (e.g. anaemia, neutropaenia, thrombocytopaenia). Dose reduction or interruption may be necessary in up to 40% of patients due to dermatologic toxicity; granulocyte colony-stimulating factor (G-CSF) can be used to ameliorate marrow suppression. Renal toxicity as seen by increased serum creatinine also may occur, which may require ganciclovir dose modification. Other toxic reactions include CNS effects, gastrointestinal dysfunction, thrombophlebitis, and elevated liver enzymes.

The main toxicity of foscarnet is decreased renal function; up to 30% of patients experience an increase in serum creatinine levels. Renal toxicity, as well as foscarnet binding to divalent metal ions such as calcium, leads to metabolic abnormalities in about one-third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures or cardiac dysrhythmias can occur. Abnormal liver transaminases and CNS symptoms can also occur. Valganciclovir causes myelosuppression.

### ***Prevention of Recurrence***

In HIV-infected children with CMV disease, following initial induction therapy, lifetime chronic suppressive maintenance therapy for CMV (secondary prophylaxis) is required; detailed recommendations can be found in *Chapter VI.: Recommendations for Adult and Paediatric Opportunistic Infections Prophylaxis*. The safety of discontinuation of secondary prophylaxis following immune reconstitution with HAART in children has not been studied extensively.

## ***HERPES SIMPLEX VIRUS (HSV) DISEASE***

### ***Epidemiology***

Neonatal transmission of HSV occurs primarily through exposure of the infant to HSV-infected maternal genital fluids during passage through the birth canal, by ascending infection, or through use of invasive

procedures, such as foetal scalp monitoring, that disrupt foetal skin integrity during labour. Congenital (*in utero*) HSV acquisition is rare, but can result in devastating coetaneous, ocular, and CNS damage. The risk of neonatal HSV infection is greatest when an infant is born to a woman with primary HSV infection. Genital shedding of HSV at the time of delivery is associated with increased risk of transmission, and prolonged rupture of membranes (greater than six hours) also increases the risk of HSV transmission to the infant, likely as a consequence of ascending HSV infection from the cervix. Caesarean delivery significantly lowers the risk of transmission.

The seroprevalence of HSV in pregnant Jamaican women in 1986 was 91%.<sup>45</sup> The incidence of congenital HSV infection in children in the Caribbean is unknown. Recurrent or persistent HSV infection is the AIDS-indicator condition in approximately 6% of HIV-infected children in Jamaica.<sup>46</sup> As in HIV-infected adults, HIV-infected children may have more frequent and severe episodes of HSV reactivation. About 5% to 10% of moderately to severely immunosuppressed children with primary gingivostomatitis develop frequent recurrences that can be associated with severe ulcerative disease and symptoms similar to primary infection. Children with HIV infection can also have more prolonged shedding of virus with both primary and re-activation HSV infection than children without HIV infection.

### ***Clinical Manifestations***

Neonatal HSV can present as disseminated multi-organ disease (occurring in about 25% of neonates with HSV infection); localised disease of the CNS (approximately 35% of neonates); or disease localised to the skin, eyes, and mouth (approximately 40% of neonates). Infants with disseminated disease generally present after the first week of life; encephalitis occurs in the majority of these infants. Vesicular rash is the most predominant presentation in children with localised skin, eye, or mouth disease, and is less frequent in children with CNS or disseminated disease. Localised disease generally presents at age ten to eleven days, and even with treatment, neonates with skin lesions may have coetaneous recurrences during the first six months after treatment.

Outside of the neonatal period, the most common presentation of HSV infection in children is orolabial disease. Fever, irritability, tender submandibular lymphadenopathy, and superficial, painful ulcers in the gingival and oral mucosa and peri-oral area characterise primary HSV gingivostomatitis. HIV-infected children who develop primary infection when they are immunocompromised can develop severe local lesions or, more rarely, disseminated HSV with visceral involvement and generalised skin lesions with primary infection. Other sites of involvement in severely immunocompromised HIV-infected children with include the oesophagus, CNS, genital disease, and disseminated disease involving the liver, adrenals, lung, kidney, spleen, and brain.

### ***Diagnosis***

Clinical diagnosis is based on the typical appearance of vesicles and ulcers. The virus can be isolated in culture, and can usually be detected in tissue culture cells within one to three days.

For the diagnosis of neonatal HSV infection, culture specimens should be obtained from blood as well as skin vesicles, mouth or nasopharynx, eyes, urine, and stool or rectum; positive cultures from any of the latter sites more than forty-eight hours after birth indicates viral replication rather than contamination after intrapartum exposure.

Direct immunofluorescence for HSV antigen can be done on cells collected from skin, conjunctiva, or mucosal lesion scrapings. Giemsa staining (Tzanck preparation) of lesion cell scrapings may show multinucleated giant cells and eosinophilic intranuclear inclusions, but this does not differentiate HSV type or HSV from varicella zoster virus (VZV) infection, and is not routinely recommended.

Definitive diagnosis of HSV oesophagitis requires endoscopy with biopsy (histologic evidence of multinucleated giant cells with intranuclear viral inclusion) and culture.

### ***Treatment Recommendations***

Acyclovir is the drug of choice for treatment of HSV in infants and children, regardless of HIV infection status. Neonatal HSV disease should be treated with high-dose intravenous acyclovir given for twenty-one days for CNS and disseminated disease and for fourteen days for skin, eye, and mouth disease. Disseminated HSV disease or encephalitis outside of the neonatal period should be treated with acyclovir for twenty-one days.

HIV-infected children with symptomatic HSV gingivostomatitis should be treated with either intravenous or oral acyclovir for seven to fourteen days. Foscarnet may be used for acyclovir resistant HSV infection.

### ***Monitoring and Adverse Events***

Primary toxicities of acyclovir are phlebitis, renal toxicity, nausea, vomiting, and rash. In infants receiving high-dose acyclovir for neonatal disease, the major toxicity is neutropaenia (absolute neutrophil count of  $<1,000/\text{mm}^3$ ).

The main toxicity of foscarnet is decreased renal function; up to 30% of patients experience an increase in serum creatinine levels. Renal toxicity, as well as foscarnet binding to divalent metal ions such as calcium, leads to metabolic abnormalities in about one-third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures or cardiac dysrhythmias can occur. Abnormal liver transaminases and CNS symptoms can also occur.

## ***VARICELLA ZOSTER VIRUS (VZV) DISEASE***

### ***Epidemiology***

Varicella has the potential to cause greater morbidity and mortality in HIV-infected immunocompromised children than among the general population of children.

It is unknown whether mother-to-child VZV transmission occurs more frequently in HIV-infected women with primary varicella.

VZV can be transmitted to the foetus in later gestation, resulting in neonatal varicella. When the mother develops varicella from four days before to two days after delivery, without passive antibody prophylaxis, the attack rate for infants is about 20%, and mortality approximately 30%. In contrast, if maternal varicella precedes delivery long enough to allow the transfer of VZV IgG antibodies across the placenta, infants may be born with coetaneous varicella lesions or develop them in the first five days of life, but they are generally not at risk for serious complications.

Zoster occurs only in children previously infected with varicella. Zoster is unusual in HIV-infected children who had primary varicella infection when their CD4+ T cell counts were normal or mildly suppressed. However, in HIV-infected children with low CD4+ T cell counts (e.g. CD4+ T cell count of  $<15\%$ ) at the time of primary varicella, the rate of subsequent zoster may be as high as 70%. As in adults, current CD4+ T cell count in children correlates with the frequency of zoster recurrences.

### ***Clinical Manifestations***

Congenital varicella infection is characterised by cicatricial skin scarring, limb hypoplasia, neurologic (microcephaly, cortical atrophy, seizures, and mental retardation), eye (chorioretinitis, microphthalmia, and cataracts), and renal (neurogenic bladder, hydroureter, hydronephrosis) abnormalities.

More severe disease may occur in HIV-infected children with lower CD4+ T cell counts not receiving ART. Both the duration of disease may be longer and the rate of complications is still higher than in normal children hospitalised with varicella.

HIV-infected children may also develop chronic infection with continued appearance of new lesions for more than one month after primary or recurrent VZV infection. The lesions are characteristically varicelliform at onset but evolve into nonhealing ulcers that become necrotic, crusted, and hyperkeratotic.

The classical clinical presentation of varicella, a generalised pruritic vesicular rash and fever, is diagnostic. However, persistent lesions may be atypical and lack a vesicular component. The classical clinical presentation of zoster, a frequently painful vesicular eruption with a dermatomal distribution, is diagnostic. However, less typical rashes, including those that extend beyond dermatomal boundaries or that are bilaterally distributed or are generalised, may also represent zoster in HIV-infected children.

HIV-infected children may have recurrent episodes of re-activated VZV infection that present with a disseminated rash more similar to chickenpox than zoster but without visceral dissemination; they may have multiple episodes of recurrent disease. VZV should be suspected in children with unilateral vesicular rashes, retinitis when CMV cannot be implicated, or with progressive and otherwise unexplained encephalitis and a history of previous varicella.

### ***Diagnosis***

Clinical diagnosis of varicella and zoster infections is based on the typical appearance of generalised pruritic vesicular rash and fever in the former and a frequently painful vesicular rash in a dermatomal pattern in the latter.

Direct immunofluorescence for VZV antigen can be done on cells collected from skin, conjunctiva, or mucosal lesion scrapings. Giemsa-staining (Tzanck preparation) of cell scrapings from lesions is nonspecific, as detection of multinucleated giant cells is suggestive of VZV but is also seen with HSV infection. The optimal sensitivity of these methods requires obtaining cells from the base of a lesion after unroofing a fresh vesicle.

### ***Treatment Recommendations***

Acyclovir is the drug of choice for treatment of VZV infection in HIV-infected children. With primary varicella, acyclovir should be initiated as soon as possible after initial lesions appear. New lesions may continue to appear for seventy-two hours after initiation of acyclovir and crusting of all lesions may take five to seven days.

Intravenous acyclovir is recommended for treatment of primary varicella in HIV-infected children with moderate or severe immunosuppression, or who have high fevers or numerous or deep, necrotic, or haemorrhagic skin lesions. Oral administration should be used only for treatment of primary varicella in HIV-infected children with normal or only slightly decreased CD4+ T cell counts or in children with mild disease.

Acyclovir is also the treatment of choice for zoster in HIV-infected children. With zoster, oral acyclovir can be given, as the chance for disseminated, life-threatening disease is less with zoster than varicella. Initial intravenous administration should be considered for HIV-infected children with severe immunosuppression, trigeminal nerve involvement, or extensive multidermatomal zoster.

Children who continue to develop lesions or whose lesions fail to heal may be infected with acyclovir resistant VZV. HIV-infected children with acyclovir resistant VZV can be treated with intravenous foscarnet.

### ***Monitoring and Adverse Events***

Primary toxicities of acyclovir are phlebitis, renal toxicity, nausea, vomiting, and rash. In infants receiving high-dose acyclovir for neonatal HSV disease, the major toxicity is neutropaenia (absolute neutrophil count of  $<1,000/\text{mm}^3$ ).

The main toxicity of foscarnet is decreased renal function; up to 30% of patients experience an increase in serum creatinine levels. Renal toxicity, as well as foscarnet binding to divalent metal ions such as calcium, leads to metabolic abnormalities in about one-third of patients, and serious electrolyte

imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures or cardiac dysrhythmias can occur. Abnormal liver transaminases and CNS symptoms can also occur.

## ***HUMAN PAPILLOMAVIRUS (HPV) DISEASE***

### ***Epidemiology***

HPV infects coetaneous and mucosal squamous epithelium. There are over 100 distinct types of HPV, nearly half first identified in the genital epithelium. They can be categorised on the basis of the site at which they occur (genital versus coetaneous) and also as high- or low-risk on the basis of their potential to induce malignant proliferation (e.g. HPV 16, 18, 31, 33, and 35 are most often associated with intraepithelial neoplasia). HPV types that cause nongenital warts are usually distinct from those causing genital infections; however, genital HPV types can cause conjunctival, nasal, oral, and laryngeal warts. Children with compromised cellular immunity, such as those seen with HIV infection, may have intense and widespread appearance of warts.

Transmission of HPV-associated coetaneous warts occurs by close person-to-person contact and may be facilitated by minor trauma to the skin. HPV-associated anogenital warts are transmitted by sexual contact but also may be acquired at the time of delivery or transmission from nongenital sites. Genital warts (*condylomata accuminata*) in young children may be a sign of sexual abuse.

Mother-to-child transmission of HPV can occur. Latent HPV infection has been identified in 5% to 42% of pregnant women without HIV infection, with higher rates in pregnant women with a history of sexually transmitted infections (STIs). In nonpregnant women, HPV DNA is detected more frequently among HIV-infected than -uninfected women, but data related to HPV prevalence in HIV-infected pregnant women are not available.

HPV DNA has been detected in cord blood peripheral blood cells and amniotic fluid, indicating the potential for *in utero* infection. Duration of membrane rupture has been associated with mother-to-child HPV transmission, and some studies have shown higher HPV infection rates in infants delivered vaginally than by Caesarean section. In general, no neonatal clinical abnormalities have been associated with HPV detection.

Infant laryngeal papillomas and juvenile laryngeal papillomatosis are thought to be secondary to HPV transmitted from mother to child through aspiration of infectious maternal genital secretions during delivery.

HPV can be detected in the genital tract of 13% to 60% of sexually-active adolescent girls. HPV 16 antibodies or HPV DNA were present in 31% to 39% of women age fifteen to nineteen years and in 18% of men at a Jamaican STI clinic.<sup>47</sup> The predominant risk factors for HPV infection in youth include the number of lifetime and recent partners.

While the incidence of anogenital HPV infection in sexually-active youth is high, longitudinal studies have demonstrated that up to 40% to 80% of infections in youth without HIV infection may be transient and spontaneously regress, although recurrent infections may be observed. Infection with multiple types or high-risk types of HPV (e.g. 16 and 18), older age, and duration of HPV detection for more than twelve months were risk factors for persistent infection. There are little published data regarding the rate of persistence among HIV-HPV-co-infected youth.

Persistent infection with HPV, particularly HPV 16, 18, 31, and 33, is associated with a high risk for development of cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia (AIN) and risk of cervical, vulvovaginal, and anal carcinoma in both women and men. Adolescent girls may have biologic differences from adult women, such as cervical squamous metaplasia, that could increase their

susceptibility to either development of persistent infection or disease. The risk of HPV-associated cervical abnormalities may be increased among HIV-infected youth.

### ***Clinical Manifestations***

HPV causes hyperplastic, papillomatous, and verrucous squamous epithelial lesions on skin and mucous membranes, including anal, genital, oral, nasal, conjunctiva, gastrointestinal, and respiratory tract mucosa.

Wart lesions appear as verrucous papules; lesions can also be smooth and flat or pedunculated. They may be soft, pink or white “cauliflower-like” sessile growths on moist mucosal surfaces (condylomata accuminata), or keratotic lesions on squamous epithelium of the skin, with a thick horny layer. They may resemble common papular warts that are flesh-coloured, 1mm to 4mm, dome-shaped papules or flat-topped papules that appear macular to slightly raised and can occur on either moist mucus membrane surfaces or skin. Most frequently, the hands, feet, face, and genitalia are involved.

### ***Diagnosis***

Most coetaneous and anogenital warts can be diagnosed by physical examination.

### ***Treatment Recommendations***

There are a number of possible treatments for HPV-associated skin and external genital lesions; no one treatment is ideal for all patients or all lesions, and treatment must be tailored to the individual patient.

Standard topical therapy for HPV-associated lesions in HIV-infected children is often ineffective. Treatment can induce wart-free periods but the underlying viral infection may persist and result in recurrence. Additionally, topical treatments seldom work in patients with large or extensive lesions. However, individual lesions can be destroyed using cryotherapy or electrodesiccation.

Topical treatments include podofilox solution and gel (0.5%) (antimitotic agent), imiquimod cream (5%) (topical immune enhancer that stimulates production of interferon and other cytokines), trichloroacetic or bichloroacetic acid 80% to 95% aqueous solution (caustic agents that destroy warts by chemical coagulation of proteins), and podophyllin resin (contains antimitotic compounds and mutagens).

Acid cauterisation and podophyllin resin require application by a healthcare provider. Acid cauterisation should be discontinued if there has not been significant improvement after three treatment sessions or complete clearance has not occurred after six treatments.

Individual lesions can be removed using cryotherapy or electrodesiccation. Cryotherapy (application of liquid nitrogen or dry ice) must be applied until each lesion is thoroughly frozen. Treatment may be repeated every one to two weeks up to four times. Curettage, electrosurgery, scissor excision, or laser vapourisation may also be effective.

Management of anogenital HPV infection accompanied by cytologic changes indicating dysplasia/carcinoma in children/adolescents is analogous to that for the adult population.

## ***HEPATITIS B (HBV) DISEASE***

### ***Epidemiology***

An important mode of HBV acquisition by children is perinatal, or mother-to-infant transmission. All pregnant women, including HIV-infected women, should be tested for hepatitis B surface antigen (HBsAg) during an early prenatal visit. Testing should be repeated in late pregnancy for HBsAg-negative women at high-risk for HBV infection (e.g. injection drug users, those with intercurrent STIs, those with multiple sexual partners).

One study in Jamaica showed evidence of HBV infection in 21% of HIV-infected women.<sup>48</sup> It is not known whether HIV-HBV-co-infected women are more likely to transmit HBV to their infants than women with HBV who are HIV-uninfected. All infants born to known HIV-HBV-co-infected women

should receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) within twelve hours of birth, the second dose of vaccine at age one to two months, and the third dose at age six months. Postvaccination testing for antibody to HBsAg (anti-HBs) and HBsAg should be performed at age nine to fifteen months, and infants found to be anti-HBs- and HBsAg-negative should be revaccinated.

Evidence of hepatitis B infection was found in 3.2% of sixty-three children from the Dominican Republic given blood transfusions during 1983 to 1987.<sup>49</sup> HIV-infected children may also be at risk of HBV infection through exposure to HBV-infected household contacts. Horizontal transmission may occur secondary to frequent interpersonal contact of nonintact skin or mucus membranes to blood or body fluids that contain blood, such as saliva, from sharing inanimate objects like toothbrushes. All infants and previously unvaccinated children should receive the three-dose hepatitis B vaccine as part of the recommended childhood immunisation schedule.

HIV-infected adolescents are at increased risk of HBV infection through sexual activity or injection drug use. All HBV-susceptible adolescents should be vaccinated against hepatitis B.

Risk of developing chronic HBV infection following acute infection in children without HIV infection is related inversely to age at the time of infection. In children without HIV infection, chronic HBV infection develops in up to 90% of infants, 30% of children age one to five years, and 6% of older children and adolescents who become infected with HBV. A study of HBV core antigen (HBc) found that 67% of HIV-infected women in Haiti showed no evidence that HIV infection predisposed them to chronic HBV infection.<sup>50</sup>

Chronic HBV infection can lead to chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma. Among individuals without HIV infection who are infected with HBV at birth, the lifetime risk of hepatocellular carcinoma reaches 50% for men and 20% for women; it is unknown if this risk is higher in HIV-HBV-co-infected persons.

Humoral response to hepatitis B vaccination is reduced in children with HIV infection. In several studies, only approximately 25% to 35% of HIV-infected children immunised with hepatitis B vaccine developed protective antibody titres. Younger children and those with higher CD4+ T cell counts are more likely to respond to vaccination than older, symptomatic, and immunodeficient HIV-infected children. Booster doses may increase response rates. HIV-infected infants, children, and adolescents should be tested for anti-HBs one to two months after completing the vaccination series, and if anti-HBs is negative, they should be revaccinated.

### ***Clinical Manifestations***

Most HBV infections in children are asymptomatic. Children with HIV-HBV-co-infection may have a mild acute illness followed by a smouldering, persistent chronic infection. Symptoms of lethargy, malaise, fatigue, and anorexia can occur. Jaundice may be present, and less commonly, hepatomegaly and splenomegaly.

Young children may experience a serum sickness-like prodrome marked by symmetrical arthropathy and skin lesions. Gianotti-Crosti syndrome (papular acrodermatitis), urticarial, or purpuric lesions can occur. Extrahepatic conditions associated with circulating immune complexes that have been reported with children with HBV infection include aplastic anaemia, polyarteritis nodosa, and glomerulonephritis.

### ***Diagnosis***

HBsAg is the first marker detectable in serum; it precedes the elevation of serum aminotransferases and the onset of symptoms. Anti-HBc appears two weeks after HBsAg and persists for life. Passively transferred maternal anti-HBc may be detectable in the infant up to age twelve months. IgM anti-HBc is highly specific for acute infection but may not be seen in perinatally-acquired infection.

In self-limited infections, HBsAg is eliminated in one to two months, and anti-HBs develops during convalescence. Anti-HBs indicates immunity from HBV infection. After recovery from natural

infection, both anti-HBs and anti-HBc are usually present, whereas only anti-HBs develops in response to the hepatitis B vaccine. In persons who become chronically infected (e.g. persistently positive for HBsAg [and anti-HBc] beyond twenty-four weeks), anti-HBs is not detectable. Hepatitis B “e” antigen (HBeAg) correlates with viral replication, DNA polymerase activity, increased infectivity, and increased severity of liver disease. With clearance of HBeAg, antibody to HBeAg (anti-HBe) may be detectable. Quantitative DNA assays may be helpful in evaluating response to therapy.

### ***Treatment Recommendations***

Early treatment of HBV infection, if started before integration of viral DNA into the nuclear DNA of the majority of host hepatocytes, may provide improved long-term outcome; however, whether treatment of acute HBV infection offers additional benefit over treatment once infection is identified as chronic is unknown and requires further study.

Indications for treatment of chronic HBV infection in HIV-co-infected children are the same as in HBV-infected children without HIV infection, and include: 1) evidence of ongoing viral replication, as indicated by the presence of detectable serum HBV DNA, with or without HBeAg positivity, for at least six months; 2) persistent elevation of serum transaminases (at least twice the upper limit of normal); and 3) evidence of chronic hepatitis on liver biopsy. Patients without necro-inflammation generally do not warrant antiviral therapy.

The correlates of successful therapy have not been well defined, but markers of improvement would include improved liver histology on biopsy, normalisation of hepatic transaminases, substantial decrease in HBV viral load (HBV DNA levels), and loss of e antigen with development of e antibody in patients who are HBeAg-positive. Although a decline in viral load correlates with response, no target HBV DNA level has been established as representing a successful virologic response. Monitoring for virologic response of therapy should include regular determination of serum levels of HBV DNA (if available), HBsAg, HBeAg, anti-HBe antibody, and serum transaminases.

There are three approved therapies for chronic hepatitis B in adults: interferon-alfa, lamivudine (3TC), and adefovir. Interferon-alfa and 3TC are also approved for treatment of chronic hepatitis B in children. 3TC is approved for children and adults for the treatment of compensated chronic hepatitis B associated with evidence of HBV replication and active liver inflammation, and would be the preferred therapy (as part of a fully suppressive HAART regimen) for chronic hepatitis B in HIV-infected children who require HIV therapy. In children with HIV-HBV co-infection, 3TC should not be administered as monotherapy because resistance of HIV to 3TC develops. It is essential in this situation for 3TC to be administered at the dose sufficient to suppress HIV as well as HBV (4mg/kg twice daily) in the context of a potent combination ARV regimen. Reports of clinical and laboratory exacerbations of hepatitis after discontinuation of 3TC treatment have occurred in children with HBV infection who are not infected with HIV. The optimal duration of therapy is not known, although experts recommend it for at least six months following HBeAg seroconversion.

For treatment of chronic hepatitis B in HIV-HBV-co-infected adults, some experts recommend that interferon-alfa be the therapy of choice in individuals who do not yet require ART for HIV infection to preserve use of 3TC and tenofovir (TDF) for later treatment of HIV infection. For HIV-HBV-co-infected adults who are ARV-naïve and require both HBV and HIV treatment, 3TC is considered by some experts to be the therapy of choice for HBV, given in HIV-suppressive doses and in combination with other ARVs for treatment of HIV infection. Considerations would be similar for HIV-HBV-co-infected children.

Interferon-alfa-2a or -2b is the therapy that has received the most study in HBV-infected children, and is recommended for the treatment of chronic hepatitis B with compensated liver disease in patients age two years or older who warrant treatment. Interferon-alfa therapy is contra-indicated in children with decompensated liver disease, significant cytopaenias, severe renal or cardiac disorders, and autoimmune

disease. None of the clinical studies of interferon-alfa therapy of chronic hepatitis B have specifically studied children with HIV-HBV co-infection.

For children who have not responded to interferon-alfa, treatment with interferon-beta, which shares common biologic functions with interferon-alfa but is antigenically different, can be considered.

### ***Monitoring and Adverse Events***

Extended treatment with 3TC can lead to the development of 3TC resistant HBV, with base pair substitutions at the YMDD locus of DNA polymerase. However, the emergence of variants containing the YMDD motif mutation did not necessarily prevent HBeAg seroconversion or result in significant worsening of liver histology. 3TC resistance should be suspected if HBV DNA levels increase or recur while receiving treatment.

Adverse effects of interferon-alfa in children, while frequent, are generally not severe. Toxicity is dose-related. Premedication with acetaminophen may reduce the incidence of side effects. The most common adverse effect of interferon-alfa is a flu-like syndrome that can consist of fever, chills, headache, myalgia, and arthralgia, abdominal pain, nausea, and vomiting. Fever generally appears within two to six hours after interferon injection and rarely febrile seizures have occurred; the flu-like symptoms are most severe during the first month of treatment. Relapsing cases of epistaxis (not associated with thrombocytopenia or prolonged prothrombin time) have been reported in some children, and occurred more frequently in the first months of treatment. Some children experience loss of appetite and a transient weight loss and impairment in height growth, which resolves following completion of therapy. Subtle personality changes have been reported in 42% of children that resolve when therapy is discontinued. Neutropenia, which resolves upon discontinuation of therapy, is the most common laboratory abnormality; anaemia and thrombocytopenia are less common. Some children have developed antinuclear auto-antibodies. Periodic monitoring of a complete blood count is recommended in children receiving interferon-alfa therapy. Abnormalities in thyroid function (hypo- or hyper-thyroidism) have been reported with interferon-alfa therapy; periodic monitoring of thyroid-stimulating hormone (TSH) is recommended.

Interferon should be permanently discontinued if a life-threatening toxicity occurs. For severe but non-life-threatening reactions, the drug can be temporarily discontinued, and after the reaction has resolved, treatment can be reinstated in a stepwise fashion, beginning with a maximum of 50% of the last administered dose. For moderate reactions, the dose can be reduced by 50% and then increased stepwise by 0.5MU or 1MU/m<sup>2</sup> up to the full dose once the adverse effect has resolved. The most common side effect with interferon-beta is low-grade fever.

**APPENDIX A: RECOMMENDATIONS FOR TREATMENT OF OIs IN HIV-EXPOSED AND -INFECTED CARIBBEAN INFANTS AND CHILDREN\***

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
<p><i>Pneumocystis jiroveci</i> (formerly <i>Pneumocystis carinii</i>) pneumonia (PCP)</p>	<p>TMP-SMX: TMP, 15-20mg/kg body weight <i>plus</i> SMX, 75-100mg/kg body weight, IV or po, divided in 3 or 4 doses per day (after acute pneumonitis resolved in mild-moderate disease, IV TMP-SMX may be changed to po) <b>Treatment Duration (followed by chronic suppressive therapy):</b> 21 days</p>	<p><b>Alternative Therapeutic Regimens (if TMP-SMX intolerant or clinical treatment failure after 5-7 days of TMP-SMX therapy):</b></p> <ul style="list-style-type: none"> <li>• Pentamidine, 4mg/kg body weight IV q.d is first-choice alternative regimen (pentamidine may be changed to atovaquone after 7-10 days IV therapy); or</li> <li>• Atovaquone, 15-20mg/kg body weight (max, 750mg/dose) po b.i.d with food; infants age 3-24 months may require a higher dose of 45mg/kg/day</li> </ul>	<ul style="list-style-type: none"> <li>• Dapsone, 2mg/kg body weight po q.d (max, 100mg/day) <i>plus</i> TMP, 15mg/kg body weight po t.i.d has been used in adults, but data in children are limited</li> <li>• Primaquine base, 0.3mg/kg body weight po q.d (max, 30mg/day) <i>plus</i> clindamycin, 10mg/kg body weight IV or po (max, 600mg IV and 300-450mg po) q6h has been used in adults, but data in children are not available</li> <li>• Indications for corticosteroids: <ul style="list-style-type: none"> <li>→ pO<sub>2</sub> &lt;70mmHg at room air or (A-a)DO<sub>2</sub> &gt;35mmHg</li> <li>→ <i>Prednisone dose:</i> 1mg/kg body weight po b.i.d for 5 days, then 1mg/kg body weight po q.d for 5 days, then 0.5mg/kg body weight po q.d for days 11-21</li> </ul> </li> <li>• Lifelong suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy. Safety of stopping secondary prophylaxis in children with immune reconstitution on HAART has not been studied extensively</li> </ul>
<p><i>Toxoplasma gondii</i></p>	<p><b><u>Congenital Toxoplasmosis:</u></b> Pyrimethamine loading dose: 2mg/kg body weight po q.d for 2 days, then 1mg/kg body weight po q.d for 2-6 months, then 1mg/kg body weight po t.i.w; <i>plus</i> leucovorin (folinic acid), 10mg po or IM with each dose of pyrimethamine; <i>plus</i> sulfadiazine,</p>	<p><b>For Sulfonamide-Intolerant Patients:</b> Clindamycin, 5.0-7.5mg/kg body weight (max, 600mg/dose) po or IV divided into 4 doses per day can be substituted for sulfadiazine <i>plus</i> pyrimethamine and leucovorin</p>	<ul style="list-style-type: none"> <li>• For infants born to mothers with symptomatic <i>Toxoplasma</i> infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mothers' treatment during pregnancy</li> <li>• Pyrimethamine use requires complete blood count monitoring weekly to monthly</li> <li>• TMP-SMX (TMP, 5mg/kg <i>plus</i> SMX, 25mg/kg IV or po b.i.d) has been used as an alternative to</li> </ul>

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
	<p>50mg/kg body weight po b.i.d  <b>Treatment Duration:</b> 12 months</p> <p><b>Acquired Toxoplasmosis:</b>  <b>Acute Induction Therapy (followed by chronic suppressive therapy):</b>  Pyrimethamine: loading dose, 2mg/kg body weight (max, 50mg) po q.d for 3 days, then 1mg/kg body weight (max, 25mg) po q.d; <i>plus</i> sulfadiazine, 25-50mg/kg body weight (max, 1-1.5gm/dose) po 4x q.d; <i>plus</i> leucovorin, 10-25mg po q.d, followed by chronic suppressive therapy  <b>Treatment Duration (followed by chronic suppressive therapy):</b> at least 6 weeks</p>		<p>pyrimethamine-sulfadiazine in adults, but has not been studied in children</p> <ul style="list-style-type: none"> <li>• Atovaquone (1.5gm po b.i.d) in regimens with pyrimethamine/leucovorin, with sulfadiazine alone, or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, has been used in adults, but these regimens have not been studied in children</li> <li>• Azithromycin (900-1,200mg/day) has also been used in adults combined with pyrimethamine-sulfadiazine, but has not been studied in children</li> <li>• Corticosteroids (e.g. prednisone or dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (&gt;1,000mg/dL) or if there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible</li> <li>• Lifelong suppressive therapy (secondary prophylaxis) is recommended in children following initial induction therapy. Safety of stopping secondary prophylaxis in children with immune reconstitution on HAART has not been studied extensively</li> </ul>
Cryptosporidiosis	<p><b>Effective HAART:</b> Immune reconstitution may lead to microbiologic and clinical response</p>	<p>There is no consistently effective therapy for cryptosporidiosis in HIV-infected individuals; several agents have demonstrated some efficacy in decreasing the severity of symptoms in children:</p> <ul style="list-style-type: none"> <li>• Nitazoxanide (data from immunocompetent children, treatment period, 3 days)  <i>Age 1-3 years:</i> 100mg po b.i.d</li> </ul>	<p><b>Supportive Care:</b> Hydration, correct electrolyte abnormalities, nutritional support</p>

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
		<p><u>Age 4-11 years:</u> 200mg po b.i.d; or</p> <ul style="list-style-type: none"> <li>• Paromomycin, 25-35mg/kg body weight in 2 to 4 divided doses po daily (max, 2gm q.d); or</li> <li>• Azithromycin, 10mg/kg body weight po on day 1, then 5mg/kg body weight po q.d (max, 600mg q.d)</li> </ul> <p><b>Treatment Duration:</b> Unknown</p>	
Microsporidiosis	<p><b>Effective HAART:</b> Immune reconstitution may lead to microbiologic and clinical response</p> <ul style="list-style-type: none"> <li>• Albendazole, 7.5mg/kg body weight (max, 400mg/dose) po b.i.d for intestinal or disseminated infection by <i>Microsporidia</i> other than <i>E. bienuesi</i></li> </ul> <p><b>Treatment Duration:</b> Unknown</p>		<ul style="list-style-type: none"> <li>• <b>Supportive Care:</b> Hydration, correct electrolyte abnormalities, nutritional support</li> <li>• Fumagillin recommended for treatment of diarrhoeal and ocular infections due to <i>E. bienuesi</i> in HIV-infected adults</li> </ul>
<i>Mycobacterium tuberculosis</i> (TB)	<p><b>Induction Phase (8 weeks):</b> Isoniazid (INH), 10-15mg/kg body weight (max, 300mg/day) po q.d; <i>plus</i> Rifampin (RIF), 10-20mg/kg body weight (max, 600mg/day) po q.d; <i>plus</i> Pyrazinamide (PZA), 20-40mg/kg (max, 2gm/day) body weight po q.d; <i>plus</i> Ethambutol (EMB), 15-25mg/kg body weight (max, 2.5gm/day) po q.d</p>	<ul style="list-style-type: none"> <li>• Alternative drug for RIF is rifabutin, 10-20mg/kg body weight (max, 300mg/day) po q.d (same dose is given for intermittent two or three times weekly regimen)</li> <li>• Alternative drug for EMB is streptomycin, 20-40mg/kg body weight (max, 1gm/day) IM q.d (or 20mg/kg given as intermittent b.i.w. or t.i.w. regimen)</li> <li>• Ethionamide, 15-20mg/kg body weight po (max, 1gm/day) divided into 2 or 3 doses/day should be used</li> </ul>	<ul style="list-style-type: none"> <li>• DOT should be standard of care for children with TB</li> <li>• Potential drug interactions, especially with HAART medications, must be carefully reviewed (see text)</li> <li>• In ARV-naïve child, initiate therapy for TB 4-8 weeks prior to starting HAART; for children already receiving HAART who are diagnosed with TB, the child's HAART regimen should be reviewed and altered, if needed, to ensure optimal treatment for both TB and HIV and to minimise potential toxicities and drug-drug interactions</li> <li>• For children with severe immunosuppression,</li> </ul>

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
	<p><b>Continuation Phase (for drug-sensitive TB):</b></p> <p><u>Daily:</u></p> <ul style="list-style-type: none"> <li>• INH, 10-15mg/kg body weight (max, 300mg/day) po q.d; <i>plus</i></li> <li>• RIF, 10-20mg/kg body weight (max, 600mg/day) po q.d</li> </ul> <p><b>OR</b></p> <p><u>Intermittent:</u></p> <ul style="list-style-type: none"> <li>• INH, 20-30mg/kg body weight (max, 900mg/day) po q.d given b.i.w or t.i.w; <i>plus</i></li> <li>• RIF, 10-20mg/kg body weight (max, 600mg/day) po q.d given b.i.w or t.i.w</li> </ul> <p><b>Treatment Duration (drug-sensitive TB):</b></p> <ul style="list-style-type: none"> <li>• <b>Pulmonary TB:</b> 9 months for HIV-infected child (6 months if not HIV-infected)</li> <li>• <b>Extrapulmonary TB:</b> 12 months</li> </ul>	<p>for TB meningitis</p> <p><b>Drug Resistant TB:</b></p> <p><u>Resistance to INH Alone:</u></p> <ul style="list-style-type: none"> <li>• Discontinue INH</li> <li>• RIF <i>plus</i> PZA <i>plus</i> EMB (ethionamide or streptomycin can be substituted for EMB if <i>M. tb</i> isolate is sensitive to these agents)</li> </ul> <p><u>Resistance to RIF Alone:</u></p> <ul style="list-style-type: none"> <li>• Discontinue RIF</li> <li>• INH <i>plus</i> PZA <i>plus</i> EMB <i>plus</i> streptomycin for first 2 months, followed by continuation phase of INH <i>plus</i> PZA <i>plus</i> EMB to complete 12-month course</li> </ul> <p><u>Multi-Drug Resistance (MDR-TB):</u></p> <ul style="list-style-type: none"> <li>• Therapy should be based on resistance pattern, and children should be managed in consultation with an expert consultant</li> </ul> <p><b>Treatment Duration (Drug Resistant TB):</b></p> <ul style="list-style-type: none"> <li>• <u>Single-drug INH or RIF resistant TB:</u> 12 months</li> <li>• <u>MDR-TB:</u> 12-24 months</li> </ul>	<p>continuation phase for drug-sensitive TB disease should include either q.d or t.i.w treatment; b.i.w regimens should <i>not</i> be used because they may lead to rifamycin resistance in immunosuppressed patients</p> <ul style="list-style-type: none"> <li>• Pyridoxine should be given if INH is administered</li> <li>• Adjunctive treatment with corticosteroids is indicated for children with CNS disease and may be considered for children with pleural or pericardial effusions, severe miliary disease, significant endobronchial disease, or severe IRS (see text)</li> <li>• Children receiving EMB who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and colour discrimination if available</li> <li>• Thiacetazone can cause severe or fatal reactions in HIV-infected children including rash and aplastic anaemia and should not be used</li> <li>• For drug resistant strains, at least 2 drugs to which the isolate is susceptible should be given (minimum of 3 drugs should be given through the continuation phase of therapy)</li> </ul> <p><b>For MDR-TB, Second-Line Drugs Include:</b></p> <ul style="list-style-type: none"> <li>• Amikacin, 15-30mg/kg body weight (max, 1gm/day) IM q.d</li> <li>• Ciprofloxacin, 10-15mg/kg body weight po b.i.d (max, 1.5gm/day); levofloxacin, 500-1,000mg po q.d; or moxifloxacin, 400mg po q.d (fluoroquinolones are not labelled for use in children &lt;age 18 years due to concerns regarding potential effects on cartilage; use in younger persons requires an assessment of potential risks and benefits)</li> </ul>

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
<p><i>Mycobacterium avium</i> Complex (MAC)</p>	<p><b>Initial Treatment (at least 2 drugs):</b></p> <ul style="list-style-type: none"> <li>• Clarithromycin, 7.5-15mg/kg body weight (max, 500mg/dose) po b.i.d; <i>plus</i></li> <li>• EMB, 15-25mg/kg body weight (max, 2.5gm/day) po q.d;</li> <li>• followed by chronic suppressive therapy</li> </ul> <p><b><u>For Severe Disease, Add:</u></b></p> <ul style="list-style-type: none"> <li>• Rifabutin, 10-20mg/kg body weight (max, 300mg/day) po q.d</li> </ul>	<p>Azithromycin, 10-12mg/kg body weight (max, 500mg/day) po q.d if intolerant to clarithromycin</p> <p><b><i>If Rifabutin Cannot Be Administered (or if a fourth drug is needed for patients with more severe symptoms or disseminated disease):</i></b></p> <ul style="list-style-type: none"> <li>• Ciprofloxacin, 20-30mg/kg body weight (max, 1.5gm/day) IV or po q.d); <b>OR</b></li> <li>• levofloxacin, 500mg po q.d; <b>OR</b></li> <li>• amikacin, 15-30mg/kg body weight IV in 1 or 2 divided doses per day (max, 1.5gm/day)</li> </ul>	<ul style="list-style-type: none"> <li>• Combination therapy with a minimum of 2 drugs is recommended</li> <li>• Children receiving EMB who are old enough to undergo routine eye testing should have monthly monitoring of visual acuity and colour discrimination if available</li> <li>• Fluoroquinolones (e.g. ciprofloxacin, levofloxacin) are not labelled for use in children &lt;age 18 years due to concerns regarding potential effects on cartilage; use in younger persons requires an assessment of potential risks and benefits</li> <li>• Lifelong suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial therapy. Safety of stopping secondary prophylaxis in children with immune reconstitution on HAART has not been studied extensively</li> <li>• If rifabutin is used, potential drug interactions, especially with HAART medications, must be carefully reviewed (see text)</li> </ul>
<p>Syphilis</p>	<p><b><u>Congenital:</u></b> <b><i>Proven or Highly Probable Disease:</i></b></p> <ul style="list-style-type: none"> <li>• Aqueous crystalline penicillin G, 100,000-150,000U/kg body weight per day, administered as 50,000U/kg body weight IV q12h for the first 7 days of life then q8h for a total of 10 days</li> <li>• If diagnosed after age 1 month, aqueous penicillin G, 200,000-</li> </ul>	<p><b><u>Congenital:</u></b> <b><i>Alternative for Proven or Highly Probable Disease (less desirable if CNS involvement):</i></b></p> <p>Procaine penicillin G, 50,000U/kg body weight IM q.d for 10 days</p> <p><b><i>Infants with Possible Congenital Syphilis (maternal treatment and response adequate, normal physical examination, normal CSF studies, but serum quantitative nontreponemal serologic titre that is the same or 4-fold</i></b></p>	<ul style="list-style-type: none"> <li>• For treatment of congenital syphilis, repeat entire course of treatment if even 1 day of treatment is missed</li> <li>• Children with congenital syphilis should be evaluated at age 1, 2, 3, 6, and 12 months, and have nontreponemal testing at 3, 6, and 12 months after conclusion of therapy or until test becomes negative. Children with increasing titres or persistently positive titres (even if low levels) at age 6-12 months should be evaluated and considered for retreatment</li> <li>• Children and adolescents with acquired syphilis</li> </ul>

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
	<p>300,000U/kg body weight IV q6h (max, 18-24MU/day) for 10 days</p> <p><b>Acquired:</b></p> <p><b>Early Stage (primary, secondary, early latent):</b></p> <p>Benzathine penicillin, 50,000U/kg body weight (max, 2.4MU) IM for 1 dose</p> <p><b>Late Latent:</b></p> <p>Benzathine penicillin, 50,000U/kg body weight (max, 2.4MU) IM q.w for 3 doses</p> <p><b>Neurosyphilis (including ocular):</b></p> <p>Aqueous penicillin G, 200,000-300,000u/kg body weight IV q6h (max, 18-24MU/day) for 10-14 days</p>	<p><b>higher than maternal titre):</b></p> <p>Benzathine penicillin G, 50,000U/kg body weight IM in a single dose (max, 2.4MU)</p>	<p>should have clinical and serologic response monitored at 3, 6, 9, 12, and 24 months after therapy</p>
<i>Candida</i>	<p><b>Oropharyngeal:</b></p> <ul style="list-style-type: none"> <li>• Fluconazole, 3-6mg/kg body weight (max, 400mg/dose) po q.d for 7-14 days; <b>OR</b></li> <li>• Itraconazole cyclodextrin oral solution, 2.5mg/kg body weight po b.i.d (max, 200mg/day) for 7-14 days; <b>OR</b></li> <li>• Clotrimazole troches: 10mg troche po 4x q.d for 14 days; <b>OR</b></li> <li>• Nystatin suspension: 4-6mL po 4x q.d <b>OR</b> 1 to 2 200,000U flavoured pastilles po q4-5d for</li> </ul>	<p><b>Oropharyngeal (fluconazole-refractory):</b></p> <ul style="list-style-type: none"> <li>• Itraconazole cyclodextrin oral solution, 2.5mg/kg body weight po b.i.d (max, 200-400mg/day) for 7-14 days; <b>OR</b></li> <li>• Amphotericin B oral suspension, 1mL (100mg/mL) po 4x q.d for 14 days</li> </ul>	<ul style="list-style-type: none"> <li>• Itraconazole cyclodextrin oral solution should not be used interchangeably with itraconazole capsules. Itraconazole capsules are generally ineffective for treatment of oesophageal disease</li> <li>• Central venous catheters should be removed when feasible in HIV-infected children with fungaemia</li> <li>• Fluconazole should not be used for the empiric treatment of fungaemia because resistance of non-<i>albicans Candida</i> species to fluconazole has been reported <ul style="list-style-type: none"> <li>→ In uncomplicated catheter-associated <i>C. albicans</i> candidaemia, an initial course of amphotericin B followed by fluconazole to complete treatment may be used</li> </ul> </li> </ul>

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
	<p>7-14 days</p> <p><b><u>Oesophageal Disease:</u></b></p> <ul style="list-style-type: none"> <li>Fluconazole, 6mg/kg body weight po q.d on day 1, then 3-6mg/kg body weight (max, 400mg/dose) po q.d for minimum of 14-21 days; <b>OR</b></li> <li>Itraconazole cyclodextrin oral solution, 2.5mg/kg body weight po b.i.d or 5.0mg/kg body weight po q.d for minimum of 14-21 days</li> </ul> <p><b><u>Invasive Disease:</u></b></p> <p>Amphotericin B, 0.5-1.5mg/kg body weight IV q.d</p> <p><b><i>Treatment Duration:</i></b> Based on presence of deep tissue foci and clinical response in patients with candidaemia, treat until 2-3 weeks after last positive blood culture</p>	<p><b><u>Oesophageal Disease:</u></b></p> <p>Amphotericin B, 0.3-0.5mg/kg body weight IV q.d for a minimum of 7 days</p> <p><b><u>Invasive Disease:</u></b></p> <ul style="list-style-type: none"> <li>Fluconazole, 5-6mg/kg body weight IV or po b.i.d (max, 800mg/day) for minimum 4 weeks (if uncomplicated <i>C. albicans</i> candidaemia)</li> <li>Lipid formulations of amphotericin B: <ul style="list-style-type: none"> <li>→ <i>Lipid Complex</i> (Abelcet®), 5mg/kg body weight IV q.d for at least 2-4 weeks</li> <li>→ <i>Liposomal</i> (AmBisome®), 3-5mg/kg body weight IV q.d for at least 2-4 weeks</li> </ul> </li> <li>Amphotericin B (as per preferred therapy dose) <i>plus</i> flucytosine, 100-150mg/kg body weight po divided into 4 doses for severe invasive disease, especially involving CNS</li> </ul>	<ul style="list-style-type: none"> <li>Amphotericin B initiation doses: <ul style="list-style-type: none"> <li>→ <i>Mild to moderate disease:</i> Initiate at doses of 0.25-0.5mg/kg body weight IV q.d, then increase as tolerated to 0.5-1.5mg/kg body weight IV q.d</li> <li>→ <i>Severe disease:</i> Initiate treatment at target daily dose</li> </ul> </li> <li>Following stabilisation and resolution of fever on daily therapy in children with invasive disease, amphotericin B may be given as 1.5mg/kg body weight IV q.o.d</li> <li>Lipid formulation of amphotericin B may be used in patients with renal insufficiency or infusion-related toxicity to amphotericin B</li> <li>Caspofungin has been used to treat oesophageal and invasive candidiasis in adults but data in children are limited and a definitive paediatric dose has not been defined</li> <li>Flucytosine dose should be adjusted to keep drug levels 40-60µg/mL</li> </ul>

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<p><i>Cryptococcus neoformans</i></p>	<p><b><u>Mild, Isolated Pulmonary Disease:</u></b> Fluconazole, 3-6mg/kg body weight po q.d followed by chronic suppressive therapy</p> <p><b><u>Severe, Isolated Pulmonary Disease:</u></b> Amphotericin B, 0.7-1.5mg/kg body weight IV q.d (usually with an initial 2 weeks of flucytosine) until stable followed by chronic suppressive therapy with fluconazole or itraconazole</p> <p><b><u>Meningeal and Extrameningeal Disseminated Disease:</u></b> <i>Acute Therapy (minimum 2-week induction followed by consolidation therapy):</i> Amphotericin B, 0.7-1.5mg/kg body weight IV q.d <i>plus</i> flucytosine, 25mg/kg body weight po given 4x q.d <i>Consolidation Therapy (followed by chronic suppressive therapy):</i> Fluconazole, 5-6mg/kg body weight IV or po b.i.d (max, 800mg/day) for a minimum of 8 weeks or until CSF cultures are sterile</p>	<p><b><u>Mild, Isolated Pulmonary Disease:</u></b> Itraconazole, 2-5mg/kg body weight po q.d or b.i.d (max, 400mg/day), followed by chronic suppressive therapy</p> <p><b><u>Meningeal and Extrameningeal Disseminated Disease:</u></b> <i>Acute Therapy (minimum 2-week induction followed by consolidation therapy):</i> Amphotericin B, 0.7-1.5mg/kg body weight IV q.d alone</p> <ul style="list-style-type: none"> <li>Liposomal amphotericin B (AmBisome®), 3-5mg/kg body weight IV q.d (with or without an initial 2 weeks of flucytosine) in children with renal insufficiency or infusion-related toxicity to amphotericin B</li> </ul> <p><i>Consolidation Therapy (followed by chronic suppressive therapy):</i> Itraconazole, 2-5mg/kg body weight (max, 200mg/dose) IV or po b.i.d for a minimum of 8 weeks or until CSF cultures are sterile</p>	<ul style="list-style-type: none"> <li>Flucytosine dose should be adjusted to keep drug levels 40-60µg/mL</li> <li>An alternative for treatment of cryptococcal meningitis is fluconazole, 5-6mg/kg body weight IV or po b.i.d (max, 800mg/day) <i>plus</i> flucytosine, 25mg/kg body weight po given 4x q.d, but there is little data in children and toxicity of this regimen limits its utility</li> <li>In cases of refractory cryptococcal meningitis with failure of systemic therapy, intrathecal or intraventricular amphotericin B has been used</li> <li>Oral acetazolamide should not be used for reduction of elevated intracranial pressure in cryptococcal meningitis</li> <li>CSF cryptococcal antigen titres &gt;1:8 suggest failure or relapse</li> <li>Lifelong suppressive therapy (secondary prophylaxis) with fluconazole is recommended in children and adults following initial therapy. Safety of stopping secondary prophylaxis in children with immune reconstitution on HAART has not been studied extensively</li> </ul>

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<i>Histoplasma capsulatum</i>	<p><b><u>Mild Disseminated Disease:</u></b> Intraconazole, 4-10mg/kg body weight IV or capsules po b.i.d for 3 days (max, 600mg/day), followed by 2-5mg/kg body weight (max, 200mg/dose) po b.i.d for at least 12-16 weeks followed by chronic suppressive therapy</p> <p><b><u>Severe Disseminated Disease:</u></b> <i>Acute Therapy (minimum 2-3 weeks induction until improved, followed by consolidation therapy; meningitis should be treated with 12-16 weeks of amphotericin):</i> Amphotericin B, 1mg/kg body weight IV q.d until stable (a minimum 2-3 weeks) <i>Consolidation Therapy (followed by chronic suppressive therapy):</i> Itraconazole capsules, 2-5mg/kg body weight (max, 200mg/dose) po b.i.d given for 3-6 months</p>	<p><b><u>Mild Disseminated Disease:</u></b> Fluconazole, 5-6 mg/kg body weight IV or po b.i.d (max, 800mg/day) for at least 12-16 weeks followed by chronic suppressive therapy</p> <p><b><u>Severe Disseminated Disease:</u></b> <i>Acute Therapy (minimum 2-3 weeks induction until improved, followed by consolidation therapy; meningitis should be treated with 12-16 weeks of amphotericin):</i> Liposomal amphotericin B (AmBisome®), 3-5mg/kg body weight IV q.d in children with renal insufficiency or infusion-related toxicity to amphotericin B</p>	<p>Lifelong suppressive therapy (secondary prophylaxis) with itraconazole is recommended in children and adults following initial therapy. Safety of stopping secondary prophylaxis in children with immune reconstitution on HAART has not been studied extensively</p>
<i>Coccidioides immitis</i>	<p><b><u>Diffuse Pulmonary or Disseminated Non-Meningitic Disease:</u></b> Amphotericin B, 0.5-1.0mg/kg body weight IV q.d until clinical improvement (minimum of several weeks), followed by chronic suppressive therapy with fluconazole or itraconazole</p> <p><b><u>Meningeal Infection:</u></b></p>	<p><b><u>Diffuse Pulmonary or Disseminated Non-Meningitic Disease (in stable patient):</u></b></p> <ul style="list-style-type: none"> <li>• Fluconazole, 5-6mg/kg body weight IV or po b.i.d (max, 800mg/day), followed by chronic suppressive therapy</li> <li>• Itraconazole, 4-10mg/kg body weight IV or po b.i.d for 3 days, followed by 2-5mg/kg body weight po b.i.d (max,</li> </ul>	<ul style="list-style-type: none"> <li>• Surgical debridement of bone and lung lesions may be helpful</li> <li>• Lifelong suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is recommended in children and adults following initial induction therapy. Safety of stopping secondary prophylaxis in children with immune reconstitution on HAART has not been studied extensively</li> </ul>

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	<p>Fluconazole, 5-6mg/kg body weight IV or po b.i.d (max, 800mg/day), followed by chronic suppressive therapy</p>	<p>400mg/day), followed by chronic suppressive therapy</p> <p><b><u>Meningeal Infection (unresponsive to fluconazole):</u></b></p> <p>Amphotericin B <i>plus</i> intrathecal amphotericin B, followed by chronic suppressive therapy</p>	
<p>Cytomegalovirus (CMV)</p>	<p><b><u>Symptomatic Congenital Infection:</u></b></p> <p>Ganciclovir, 6mg/kg body weight IV q12h for 6 weeks</p> <p><b><u>Disseminated Disease and Retinitis:</u></b></p> <p><b><i>Induction Therapy (followed by chronic suppressive therapy):</i></b></p> <p>Ganciclovir, 5mg/kg body weight IV q12h for 14-21 days (may be increased to 7.5mg/kg body weight IV b.i.d), then 5mg/kg per day for 5 to 7 days per week for chronic suppression</p>	<p><b><u>Disseminated Disease and Retinitis:</u></b></p> <p><b><i>Induction Therapy (followed by chronic suppressive therapy):</i></b></p> <p>Foscarnet, 60mg/kg body weight IV q8h for 14-21 days, then 90-120mg/kg q.d for chronic suppression</p> <p><b><i>Alternative for Retinitis (followed by chronic suppressive therapy):</i></b></p> <ul style="list-style-type: none"> <li>• IV ganciclovir <i>plus</i> IV foscarnet (at above induction doses) – may be considered as initial induction therapy in children with sight-threatening disease</li> <li>• <b><i>Older Children:</i></b> Ganciclovir intraocular implant <i>plus</i> oral ganciclovir, 30mg/kg t.i.d or if old enough to receive adult dosing, oral valganciclovir, 900mg po q.d</li> </ul>	<ul style="list-style-type: none"> <li>• Valganciclovir is used in adults for treatment of CMV retinitis: induction dosing in adults is 900mg po b.i.d for 14-21 days, followed by chronic suppressive therapy; however, data on valganciclovir dosing in children is unavailable</li> <li>• Cidofovir is also used for treatment of CMV retinitis in adults: induction dosing in adults is 5mg/kg body weight IV q.w for 2 weeks, followed by chronic suppressive therapy; however, data on dosing in children is unavailable</li> <li>• Intravitreal injections not practical for most children</li> <li>• Intraocular implant should not be used in children &lt;age 3 years due to small size of eyes</li> <li>• Lifelong suppressive therapy (secondary prophylaxis) is recommended in children and adults following initial induction therapy. Safety of stopping secondary prophylaxis in children with immune reconstitution on HAART has not been studied extensively</li> </ul>

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Herpes Simplex Virus (HSV)	<p><b><u>Neonatal CNS or Disseminated Disease:</u></b> Acyclovir, 20mg/kg body weight IV t.i.d for 21 days</p> <p><b><u>Neonatal Skin, Eye, or Mouth Disease:</u></b> Acyclovir, 20mg/kg body weight IV t.i.d for 14 days</p> <p><b><u>CNS or Disseminated Disease in Children Outside the Neonatal Period:</u></b> Acyclovir, 10mg/kg body weight IV t.i.d for 21 days</p> <p><b><u>Moderate to Severe Symptomatic Gingivostomatitis:</u></b> Acyclovir, 5-10mg/kg body weight IV t.i.d for 7-14 days</p> <p><b><u>Genital Herpes (Adults and Adolescents):</u></b> Acyclovir, 20mg/kg body weight (max, 400mg/dose) po t.i.d for 7-10 days.</p>	<p><b><u>Acyclovir-Resistant HSV Infection:</u></b> Foscarnet, 40mg/kg body weight given IV t.i.d or 60mg/kg body weight given IV b.i.d</p> <p><b><u>Mild Symptomatic Gingivostomatitis:</u></b> Acyclovir, 20mg/kg body weight (max, 400mg/dose) po t.i.d for 7-14 days</p>	<ul style="list-style-type: none"> <li>• <i>For neonatal CNS disease:</i> Repeat CSF HSV DNA PCR should be performed at day 19-21 of therapy; do not stop acyclovir until repeat CSF HSV DNA PCR is negative</li> <li>• Suppressive secondary prophylaxis with oral acyclovir can be considered for children with severe and recurrent gingivostomatitis</li> </ul>
Varicella Zoster Virus (VZV)	<p><b><u>Primary Varicella (Chickenpox):</u></b> <i>Children with Moderate or Severe Immune Suppression, High Fever, or Necrotic Lesions:</i> Acyclovir, 10mg/kg body weight IV t.i.d for 7 days after no new lesions</p> <p><i>Children with Mild Immune Suppression and Mild Disease:</i></p>	<p><b><i>For Patients Not Responding to Acyclovir:</i></b> Foscarnet, 40-60mg/kg body weight IV t.i.d for 7-10 days</p>	<p>Some experts base IV acyclovir dosing in children <math>\geq</math> age 1 year on body surface area (500mg/m<sup>2</sup>/dose IV q8h) instead of body weight</p>

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
	<p>Acyclovir, 20mg/kg body weight po (max, 200mg/dose) 4x q.d, continued for 7 days after no new lesions</p> <p><b><u>Zoster:</u></b></p> <p><i>Children with Severe Immune Suppression, Trigeminal Nerve Involvement, or Extensive Multi-Dermatomal Zoster:</i></p> <p>Acyclovir, 10mg/kg body weight IV t.i.d for 7-10 days</p> <p><i>Children with Mild Immune Suppression and Mild Disease:</i></p> <p>Acyclovir, 20mg/kg body weight po (max, 200mg/dose) 4x q.d for 7-10 days</p>		
Human Papillomavirus (HPV)	Individual lesions can be removed by cryotherapy or electrodesiccation; may be repeated q.w to b.i.w up to 4 times	<ul style="list-style-type: none"> <li>• Podofilox solution/gel (0.5%) applied topically b.i.d for 3 consecutive days a week for up to 4 weeks</li> <li>• Imiquimod cream (5%) applied topically at night and washed off in the morning for 3 nonconsecutive days a week for up to 16 weeks</li> <li>• Trichloroacetic acid applied topically q.w for up to 3-6 weeks</li> <li>• Podophyllin resin applied topically and washed off several hours later q.w for 3-6 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Standard topical therapy in children is often ineffective</li> <li>• Cidofovir topical gel (1%) is an experimental therapy studied in HIV-infected adults, but is not commercially available and has very limited use in children; systemic absorption can occur</li> <li>• HAART has not been consistently associated with reduced risk of HPV-related cervical abnormalities in HIV-infected women</li> <li>• Laryngeal papillomatosis generally requires referral to a paediatric otolaryngologist. Treatment is directed at maintaining the airway, rather than removal of all disease. Adjuvant therapy with interferon-alfa or intralesional cidofovir is being used investigationally for invasive disease</li> </ul>

PATHOGEN	PREFERRED THERAPIES AND DURATION	ALTERNATIVE THERAPIES	OTHER OPTIONS/ISSUES
Hepatitis B Virus (HBV)	<p><b><i>For Children Who Require HIV Therapy:</i></b>            3TC, 4mg/kg body weight po (max, 150mg/dose) b.i.d as part of a fully suppressive HAART regimen for a minimum of 12 months or 6 months after HBeAg seroconversion</p> <p><b><i>For Children Who Do Not Require HIV Therapy:</i></b></p> <ul style="list-style-type: none"> <li>• Interferon-alfa, 5MU/m<sup>2</sup> body surface area subcoetaneously (max, 10MU/dose) t.i.w</li> <li>• If HBeAg-positive, recommended duration of interferon-alfa therapy is 6 months; if HBeAg-negative, a duration of 12 months or longer may be desirable</li> </ul>	Interferon-alfa, 10MU/m <sup>2</sup> body surface area subcoetaneously t.i.w for 6 months (sometimes used for retreatment of failed lower dose interferon therapy)	<ul style="list-style-type: none"> <li>• Indications for treatment include:               <ul style="list-style-type: none"> <li>→ Detectable serum HBV DNA, with or without +HBeAg, for at least 6 months;</li> <li>→ Persistent elevation of serum transaminases (at least 2x the upper limit of normal); and</li> <li>→ Evidence of chronic hepatitis on liver biopsy</li> </ul> </li> <li>• Interferon-alfa is contra-indicated in children with decompensated liver disease, significant cytopaenias, severe renal or cardiac disorders, and auto-immune disease</li> <li>• Prednisone co-administration not recommended</li> <li>• Interferon-beta 5MU/m<sup>2</sup> body surface area IM t.i.w for 6 months for children who have not responded to interferon-alpha</li> <li>• In children receiving 3TC and responding to therapy, clinical and laboratory exacerbations of hepatitis may occur if 3TC is discontinued; thus, once anti-HBV/HIV therapy has begun, it should be continued unless contra-indicated or until the child has been treated for &gt;6 months after HBeAg seroconversion and can be closely monitored on discontinuation</li> </ul>

*\*Note: Information contained in these guidelines might not represent U.S. Food and Drug Administration (FDA) approval or approved labelling for products or indications. Specifically, the terms ‘safe’ and ‘effective’ might not be synonymous with the FDA-defined legal standards for product approval. Letters and Roman numerals in parentheses after regimens indicate the strength of the recommendations and the quality of evidence supporting it.*

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