

## DISEASE SPECIFIC RECOMMENDATIONS

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

#### *Epidemiology*

PCP is caused by *Pneumocystis jiroveci*, a ubiquitous organism that is classified as a fungus but shares biological characteristics with protozoa. (*P. carinii* now refers only to the pneumocystis that infects rodents, while *P. jiroveci* refers to the distinct species that infects humans. The abbreviation “PCP” is still used to designate *Pneumocystis* pneumonia.)

PCP is widespread in the Caribbean. Among twenty Haitians studied in 1980 to 1982, PCP was among the most common OIs seen.<sup>i</sup> In a cohort of children with HIV infection in Barbados, PCP was the most common cause of death (65.2%).<sup>ii</sup> In AIDS patients in Puerto Rico, PCP (26.8%) was one of the three main diagnoses for AIDS<sup>iii</sup>.

Over 90% of cases of PCP occur in patients with CD4+ T cell counts of <200 cells/mm<sup>3</sup>. Other factors associated with a higher risk of PCP include CD4+ T cell percentage of <15%, prior episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA. The incidence of PCP has declined dramatically with widespread use of prophylaxis and effective HAART. Most cases now occur in patients unaware of their HIV infection or not receiving ongoing HIV care, or in those with advanced immunosuppression (e.g. CD4+ T cell counts of <100 cells/mm<sup>3</sup>).

#### *Clinical Manifestations*

The most common manifestations of PCP in HIV-infected persons are the subacute onset of progressive exertional dyspnea, fever, non-productive cough, and chest discomfort that worsens over a period of days to weeks. In mild cases, pulmonary examination is usually normal at rest. With exertion, tachypnea, tachycardia, and diffuse dry (*cellophane*) rales may occur. Oral thrush is a common co-infection. Fever is apparent in most cases and may be the predominant symptom in some patients. Hypoxaemia, the most characteristic laboratory abnormality, may range from mild or moderate (room air arterial oxygen [pO<sub>2</sub>] of >70mmHg or alveolar-arterial O<sub>2</sub> difference [(A-a)DO<sub>2</sub>] of <35mmHg) to more severe levels (pO<sub>2</sub> of <70mmHg or [A-a]DO<sub>2</sub> of >35mmHg). Oxygen desaturation with exercise is suggestive of an abnormal A-a gradient, but is non-specific. The chest radiograph typically demonstrates diffuse, bilateral, symmetrical interstitial infiltrates emanating from the hili in a butterfly pattern; however, patients with very early disease may have a normal chest x-ray. In addition, atypical presentations with nodules, asymmetric disease, blebs and cysts, upper lobe localisation, and pneumothorax can occur. Cavitation or pleural effusion is uncommon in the absence of other pulmonary pathogens or malignancy, and the presence of a pleural effusion may be a clue to an alternative diagnosis. Between 13% and 18% of patients with documented PCP have had another concurrent cause of pulmonary dysfunction such as TB, KS, or bacterial pneumonia. Pneumothorax in a patient with HIV infection should raise the suspicion of PCP.

#### *Diagnosis*

Because the clinical presentation, blood tests, or chest x-ray are not pathognomonic for PCP and the organism cannot be routinely cultivated, histopathologic demonstration of organisms in tissue, bronchoalveolar lavage fluid, or induced sputum samples are required for a definitive diagnosis. Spontaneously-expectorated sputum has very low sensitivity and should not be submitted to the laboratory to diagnose PCP. Cresyl violet, Giemsa, Diff-Quik, and Wright stains detect both the cyst and trophozoite forms but do not stain the cyst wall, while Gomori's Methenamine Silver, Gram-Weigert, and Toluidine Blue stain the cyst wall. Many laboratories prefer direct immunofluorescent staining. Stained respiratory tract samples obtained by various methods indicate the following relative diagnostic sensitivities: induced sputum <50% to >90% (the sensitivity and specificity depends heavily on the quality of the specimens and the experience of the microbiologist or pathologist); bronchoscopy with bronchoalveolar lavage 90% to 99%; transbronchial biopsy 95% to 100%; and open lung biopsy 95% to 100%.

Because many processes can present with similar clinical manifestations, a specific diagnosis of PCP should be sought rather than relying on a presumptive diagnosis. Treatment can be initiated prior to making a definitive diagnosis since organisms persist in clinical specimens for days or weeks after effective therapy is initiated.

### ***Treatment Recommendations***

Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of first choice (see *Appendix B*). The dose must be adjusted for abnormal renal function. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended due to questionable efficacy and some evidence of a higher failure rate. Oral outpatient therapy of TMP-SMX is highly effective in patients with mild to moderate disease. Patients who develop PCP despite TMP-SMX prophylaxis are usually effectively treated with standard doses of TMP-SMX.

Patients with documented PCP and moderate to severe disease as defined by  $pO_2$  of  $<70\text{mmHg}$  or  $[A-a]DO_2$  of  $>35\text{mmHg}$  should receive corticosteroids as early as possible and certainly within seventy-two hours after starting specific PCP therapy. If steroids are started at a later time, it is not clear that they provide any benefit, although most clinicians would use them in such circumstances for patients with severe disease. The preferred corticosteroid dose and regimen is prednisone 40mg by mouth twice daily for days one through five, 40mg daily for days six through ten, and 20mg daily for days eleven through twenty-one. Methylprednisolone at 75% of the respective prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens include: a) dapsone plus TMP for mild to moderate disease (this regimen may have similar efficacy and fewer side effects than TMP-SMX but is less convenient because of the number of pills); b) primaquine plus clindamycin (this regimen is also effective in mild to moderate disease, and the clindamycin component can be administered intravenously for more severe cases; however, primaquine is only available orally); c) intravenous (IV) pentamidine (generally the drug of second choice for severe disease); d) atovaquone suspension (this is less effective than TMP-SMX for mild to moderate disease but has fewer side effects); and e) trimetrexate with leucovorin (this is less effective than TMP-SMX but may be used if the latter is not tolerated and an IV regimen is needed), although leucovorin must be continued three days after the last trimetrexate dose. The addition of dapsone, SMX, or sulfadiazine to trimetrexate may improve efficacy based on the sequential enzyme blockade of folate metabolism, although there are no study data available to confirm this.

Aerosolised pentamidine should not be used for the treatment of PCP because of limited efficacy and more frequent relapse.

The recommended duration of therapy for PCP is twenty-one days. Overall, the probability and rate of response to therapy depends on the agent used, number of prior episodes, severity of illness, degree of immunodeficiency, and timing of initiation of therapy.

Although the overall prognosis of patients whose degree of hypoxaemia requires ICU admission or whose mechanical ventilation remains poor, survival in up to 40% of patients requiring ventilatory support has been reported in recent years. Because long-term survival is possible for those patients for whom HAART is effective, many patients with AIDS and severe PCP should be offered ICU admission or mechanical ventilation when appropriate, e.g. when they have good functional status and no concurrent life-threatening processes.

Because of the potential for additive or synergistic toxicities associated with anti-PCP and HAART, many experts delay initiation of HAART until after the completion of anti-PCP therapy despite some suggestion of potential benefit for early HAART. An inflammatory IRS has been described for PCP and may complicate the concurrent administration of anti-PCP treatment and HAART.

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

Careful monitoring during therapy is important to evaluate response to treatment and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially when therapy has been with an agent other than TMP-SMX or was shortened for toxicity. PCP prophylaxis should be initiated promptly and maintained until the CD4+ T cell count rises to  $>200$  cells/mm<sup>3</sup>. If PCP occurred at a CD4+ T cell count of  $>200$  cells/mm<sup>3</sup>, it may be prudent to maintain PCP prophylaxis for life regardless of the CD4+ T cell response, although data regarding the most appropriate approach in this setting are limited. Adverse reaction rates in patients with AIDS are high for TMP-SMX (20% to 85%), although may be less common among dark-skinned people in the Caribbean. Common adverse effects (see *Appendix D*) are rash (30% to 55%) including, rarely, Stevens-Johnson syndrome; fever (30% to 40%); leukopaenia (30% to 40%); thrombocytopaenia (15%); azotaemia (1% to 5%); hepatitis (20%); and hyperkalaemia. Supportive care for common adverse effects should be tried before abandoning TMP-SMX. Rashes may often be “treated through” with antihistamines, nausea can be controlled with antiemetics, and fever can be managed with antipyretics.

The most common adverse effects of alternative therapies include methemoglobinaemia and haemolysis with dapsone or primaquine (especially in those with G6PD deficiency); rash and fever with dapsone; azotaemia, pancreatitis, hypo- or hyperglycaemia, leukopaenia, fever, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine; anaemia, rash, fever, diarrhoea, and methemoglobinaemia with primaquine and clindamycin; headache, nausea, diarrhoea, rash, fever, and transaminase elevations with atovaquone; and bone marrow suppression, fever, rash, and hepatitis with trimetrexate.

#### ***Management of Treatment Failure***

Clinical failure is defined by the lack of improvement or worsening of respiratory function documented by arterial blood gases after at least four to eight days of anti-PCP treatment.

Treatment failure attributed to treatment-limiting toxicities occurs in up to one-third of patients. Failure due to lack of drug efficacy occurs in 10% or more of those with mild to moderately severe disease. Adding or switching to another regimen is the appropriate management for treatment-related toxicity. There are no convincing clinical trials published upon which to base well-founded recommendations for the management of treatment failure due to lack of drug efficacy. It is important to wait at least four to eight days prior to switching therapy for lack of clinical improvement. In fact, in the absence of corticosteroid therapy, early and reversible deterioration within the first three to five days of therapy is typical; this is likely due to the inflammatory response caused by antibiotic-induced lysis of organisms in the lung. Other concomitant infections must be excluded as a cause for such deterioration. Bronchoscopy with bronchoalveolar lavage is optimal and should be considered whenever possible.

If TMP-SMX has failed or must be avoided for toxicity in moderate to severe disease, the common practice is to use primaquine combined with clindamycin or clindamycin plus primaquine (with or without oral dapsone) plus leucovorin. For mild disease, atovaquone is a reasonable alternative. Although one meta-analysis concluded that trimetrexate may be the most effective regimen for salvage therapy, no prospective clinical trials have evaluated the optimal approach to patients who fail therapy with TMP-SMX.

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

Patients who have a history of PCP should be administered secondary prophylaxis for life with TMP-SMX unless immune reconstitution occurs as a consequence of HAART. For patients intolerant of TMP-SMX, alternatives include dapsone, dapsone combined with pyrimethamine, atovaquone, or aerosolised pentamidine.

Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ T cell count has increased from  $<200$  cells/mm<sup>3</sup> to  $>200$  cells/mm<sup>3</sup> for at least three months as a result of antiretroviral therapy. Secondary prophylaxis should be re-introduced if the CD4+ T cell count decreases to  $<200$  cells/mm<sup>3</sup> or if PCP recurs at a CD4+ T cell count of  $>200$

cells/mm<sup>3</sup>.

### ***Special Considerations in Pregnancy***

Diagnostic considerations and indications for therapy in pregnancy are the same as in non-pregnant adults. The preferred initial therapy during pregnancy is TMP-SMX, although alternate therapies may be used if patients are unable to tolerate or are unresponsive to TMP-SMX. Neonatal care providers should be informed of maternal sulfa or dapsone therapy if used near delivery because of the theoretical increased risk of hyperbilirubinemia and kernicterus.

Pentamidine is embryotoxic but not teratogenic in rats and rabbits. Trimetrexate should not be used because of teratogenicity at low doses in multiple animal studies, foetopathy in humans associated with use of the biochemically similar agents methotrexate and aminopterin, and potential negative effects on placental and foetal growth (see *Appendix A* for information on specific drugs).

Adjunctive corticosteroid therapy should be used as indicated in non-pregnant adults. Maternal fasting and postprandial glucose levels should be monitored closely when corticosteroids are used in the third trimester, as the risk of glucose intolerance is increased.

Rates of pre-term labour and pre-term delivery are increased with pneumonia in pregnancy. Pregnant women with pneumonia after twenty weeks of gestation should be monitored for evidence of contractions.

## **TOXOPLASMA GONDII ENCEPHALITIS**

### ***Epidemiology***

Toxoplasmic encephalitis (TE), caused by the protozoan *Toxoplasma gondii*, has been documented in HIV-infected patients in and from the Caribbean.<sup>iv</sup> In a study conducted in Martinique, TE was the most frequent presenting complication of AIDS.<sup>v</sup> The disease occurs exclusively due to re-activation of latent tissue cysts; there is no transmission of the organism by person-to-person contact. The development of clinical disease is rare in patients with CD4+ T cell counts of >200 cells/mm<sup>3</sup>. The greatest risk is among patients with CD4+ T cell counts of <50 cells/mm<sup>3</sup>.

### ***Clinical Manifestations***

The most common clinical presentation of *T. gondii* infection in patients with AIDS is a focal encephalitis with headache, confusion or motor weakness, and fever. Physical examination may demonstrate focal neurological abnormalities, and, in the absence of treatment, disease progression results in seizures, stupor, and coma. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement can be seen following dissemination of infection but are rare manifestations in this patient population. Primary infection is occasionally associated with acute cerebral or disseminated disease.

### ***Diagnosis***

Computerised tomography (CT) or magnetic resonance imaging (MRI) of the brain will typically show multiple contrast-enhancing lesions, often with associated oedema. No imaging technique is completely specific in distinguishing between TE and primary CNS lymphoma.

HIV-infected patients with TE are almost uniformly seropositive for anti-*Toxoplasma* IgG antibodies. The absence of the IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-*Toxoplasma* IgM antibodies are usually absent, and quantitative antibody titers are not diagnostically useful. Definitive diagnosis of TE requires a compatible clinical syndrome; identification of one or more mass lesions by CT, MRI, or other radiographic testing; and detection of the organism in a clinical sample, e.g. by brain biopsy. However, patients suspected to have TE on the basis of serology, clinical symptoms, radiologic findings, and the absence of a likely alternative diagnosis are generally treated

empirically; confirmation of the diagnosis can be reasonably inferred from clinical and radiographic improvement in response to specific anti-*T. gondii* therapy. Brain biopsy is generally reserved for patients failing to respond to specific therapy.

In the presence of neurologic disease, the differential diagnosis includes CNS lymphoma, mycobacterial infection (especially TB), fungal infection (e.g. cryptococcosis), Chagas disease, and bacterial abscess. PML can usually be distinguished based on imaging studies, for PML lesions typically involve white matter rather than grey matter, are non-contrast enhancing, and show no mass effect.

### ***Treatment Recommendations***

The initial therapy of choice consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin. Use of leucovorin prevents the haematologic toxicities associated with pyrimethamine therapy. The preferred alternative regimen for patients unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.

For patients who cannot take an oral regimen, there are no well-studied options. There is no parenteral formulation of pyrimethamine; the only widely available parenteral sulfonamide is the SMX component of TMP-SMX. Thus, some experts will treat severely ill patients requiring parenteral therapy initially with oral pyrimethamine plus parenteral TMP-SMX or parenteral clindamycin.

The following regimens have been shown to have activity in the treatment of TE in at least two non-randomised, uncontrolled trials, though their relative efficacy compared to the above regimens is unknown: 1) atovaquone (with meals or oral nutritional supplements) plus pyrimethamine plus leucovorin; 2) atovaquone combined with sulfadiazine or, for patients intolerant of both pyrimethamine and sulfadiazine, as a single agent; and 3) azithromycin plus pyrimethamine plus leucovorin daily.

The following regimens have been reported to have activity in the treatment of TE in small cohorts of patients or in case reports of one or a few patients: clarithromycin plus pyrimethamine; 5-fluoro-uracil plus clindamycin; dapsone plus pyrimethamine plus leucovorin; and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin.

Acute therapy should be continued for at least six weeks if there is clinical and radiologic improvement. Longer courses may be appropriate if clinical or radiologic disease is extensive or response is incomplete at six weeks. Adjunctive corticosteroids (e.g. dexamethasone) should be administered when clinically indicated only for treatment of a mass effect due to focal lesions or associated oedema. Because of the potential immunosuppressive effects of corticosteroids, they should be discontinued as soon as clinically feasible. Patients receiving corticosteroids should be closely monitored for the development of other OIs including CMV retinitis and TB. Anticonvulsants should be administered to patients with a history of seizures, but should not be administered prophylactically to all patients. Anticonvulsants, if administered, should probably be continued at least through the period of acute therapy.

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

Patients should be routinely monitored for adverse events and clinical and radiologic improvement. Common pyrimethamine toxicities include rash, nausea, and bone-marrow suppression (neutropaenia, anaemia, and thrombocytopenia) that can often be reversed by increasing the dose of leucovorin to 50 to 100mg daily, administered in divided doses.

Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhoea, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhoea (including pseudomembranous colitis or diarrhoea related to *C. difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity. Drug interactions between anticonvulsants and ARV agents should be carefully evaluated and doses be adjusted according to established guidelines.

### ***Management of Treatment Failure***

For patients who fail to respond to initial therapy as defined by 1) clinical or radiologic deterioration during the first week despite adequate therapy, or 2) a lack of clinical improvement within two weeks, a brain biopsy, if not previously performed, should be strongly considered. For those who undergo brain biopsies and have confirmed histopathologic evidence of TE, a switch to an alternative regimen as previously described should be considered. Recurrence of disease during secondary maintenance therapy following an initial clinical and radiographic response is unusual if patients are adherent to their regimens.

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

Patients who have successfully completed a six-week course of initial therapy for TE should be administered lifelong suppressive therapy (e.g. secondary prophylaxis or chronic maintenance therapy) unless immune reconstitution occurs due to HAART.

Adult and adolescent patients receiving secondary prophylaxis for TE appear to be at low risk for recurrence of TE when they have successfully completed initial therapy for TE, remain asymptomatic with respect to signs and symptoms of TE, and have a sustained increase in their CD4+ T cell counts to  $>200$  cells/mm<sup>3</sup> following six months or more of HAART. Discontinuing chronic maintenance therapy among such patients is a reasonable consideration. However, secondary prophylaxis should be re-started if the CD4+ T cell count decreases to  $<200$  cells/mm<sup>3</sup>.

### ***Special Considerations in Pregnancy***

Treatment should be the same as in non-pregnant adults. Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects; therefore, it can be administered to pregnant women. Paediatric providers should be notified if sulfadiazine is continued until delivery since its use may increase the risk of neonatal hyperbilirubinemia and kernicterus.

While perinatal transmission of *T. gondii* normally occurs only with acute infection in the immunocompetent host, case reports have documented occurrences of transmission, albeit at very low rates, with re-activation of chronic infection in HIV-infected women with severe immunosuppression. Since risk of transmission with chronic infection appears low, routine evaluation of the foetus for infection with amniocentesis or cordocentesis is not indicated.

Where available, detailed ultrasound examination of the foetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be performed for HIV-infected women with suspected primary or symptomatic re-activation of *T. gondii* during pregnancy.

## ***CRYPTOSPORIDIOSIS***

### ***Epidemiology***

Cryptosporidiosis is caused by *Cryptosporidium* species, a group of protozoan parasites that infect the small bowel mucosa, and in immunosuppressed individuals, the large bowel and extraintestinal sites. Those at greatest risk for this disease are patients with advanced immunosuppression, e.g. with CD4+ T cell counts generally  $<100$  cells/mm<sup>3</sup>. Among forty Cuban patients with HIV infection, cryptosporidiosis was among the most commonly found OIs.<sup>vi</sup>

Transmission occurs through ingestion of *Cryptosporidium* oocysts. Faeces from infected animals, including humans, can contaminate water supplies and recreational water with viable oocysts despite standard chlorination. Person-to-person transmission, primarily among men who engage in oral-anal sex, has also been observed. Young children with cryptosporidial diarrhoea may also infect adults, especially in the course of nappy-changing. Scrupulous handwashing, use of barriers during anal sex, and other hygiene measures may help to prevent person-to-person transmission.

### ***Clinical Manifestations***

The most common manifestation is the acute or subacute onset of profuse, non-bloody watery diarrhoea frequently accompanied by nausea, vomiting, and lower abdominal cramping. Fever is present in approximately one-third of patients. Malabsorption is often present. Cholangitis and pancreatitis occur in patients with prolonged disease.

### ***Diagnosis***

Diagnosis of cryptosporidiosis is primarily based on microscopic identification of the oocysts in stool or tissue; there is no consensus on the optimal oocyst detection method in faecal samples. Oocysts stain red with varying intensities with a modified acid-fast technique; this technique allows for differentiation of the *Cryptosporidium* oocysts from yeasts that are similar in size and shape but are not acid-fast. Oocysts can also be detected by direct immunofluorescent or enzyme-linked immunosorbent assays. The modified acid-fast stain and fluorescein-labelled monoclonal antibody technique show comparability for diarrhoeal samples, but the immunofluorescent method is probably preferable for formed stool specimens.

In individuals with profuse diarrhoeal illness, a single stool specimen is usually adequate to make the diagnosis. In individuals with less severe disease, repeat stool sampling is recommended, although there have been no controlled studies showing the utility of three consecutive stool samples as is the case in *Giardia duodenalis* infection.

### ***Treatment Recommendations***

HAART with immune restoration (an increase of CD4+ T cell count to  $>100$  cells/mm<sup>3</sup>) is associated with complete resolution of cryptosporidiosis, and all patients with cryptosporidiosis should be offered HAART as part of the initial management of their infection.

At present, there is no consistently effective pharmacologic or immunologic therapy directed specifically against *C. parvum*. More than ninety-five interventional agents have been tried for the treatment of cryptosporidiosis with no consistent success.

Paromomycin, a non-absorbable aminoglycoside that is indicated for the treatment of intestinal amebiasis, is effective in very high doses for the treatment of cryptosporidiosis in animal models. A meta-analysis of eleven published paromomycin studies in humans reported a response rate of 67%. However, relapse was common in the few studies that evaluated this, with long term success rates of only 33%. Two randomised, controlled trials have compared paromomycin with placebos in patients with AIDS and cryptosporidiosis; modest, but statistically significant, improvement in symptoms and oocyst shedding was demonstrated in one, but no difference from the placebo was observed in the other. Thus, efficacy data do not support a recommendation for the use of paromomycin for therapy, although the drug appears to be safe.

Treatment of individuals with cryptosporidiosis should include symptomatic treatment of diarrhoea. Rehydration and repletion of electrolyte losses by either the oral or IV route is of paramount importance. Severe diarrhoea, which may be over 10L/d in patients with AIDS, often requires intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions that contain glucose, sodium bicarbonate, potassium, magnesium, and phosphorus. Treatment with antimotility agents can play an important adjunctive role in therapy, but these agents are not consistently effective. Loperamide or tincture of opiate will often palliate symptoms.

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

Patients should be closely monitored for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition and should receive supportive treatment. Total parenteral nutrition may be indicated in some patients.

### ***Management of Treatment Failure***

At this time, there are no alternatives to HAART and supportive treatment that are

demonstrated to be useful.

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

No drug regimens are currently proven to be effective in preventing the recurrence of cryptosporidiosis.

## ***ISOSPORIASIS***

### ***Epidemiology***

Isosporiasis results from ingestion of food or water contaminated by oocysts of the protozoan *Isospora belli*. Infection occurs worldwide, but the prevalence of infection is higher in tropical and subtropical regions. Infection can occur in both immunocompetent and immunocompromised hosts.

### ***Clinical Manifestations***

Infection primarily involves the small intestine. The most common clinical manifestation of the disease is diarrhoea, which can result in severe dehydration. Systemic symptoms of fever, headache, malaise, abdominal pain, vomiting, and weight loss are also common. Colitis and haematochezia are rare.

### ***Diagnosis***

The diagnosis of isosporiasis can be made by stool examination for ova and parasites. Oocysts are ovoid in shape and are 23 to 36 by 12 to 17 $\mu$ M in size. *Isospora* oocysts autofluoresce a blue-green colour under an epifluorescence microscope, enhancing their detection in wet-mount preparations. The organisms also stain red with the same modified acid-fast technique used for diagnosis of cryptosporidiosis. No commercial antigen-detection systems have been developed. Schizonts, merozoites, macrogamonts, microgamonts, microgametes, and oocysts can be demonstrated in enterocytes in biopsies of the small or large intestine. Extraintestinal infections with tissue cyst-like stages have been demonstrated in lymph nodes adjacent to the intestine in patients with AIDS.

### ***Treatment Recommendations***

Fluid support should be administered if dehydration has developed. Nutritional supplementation is indicated for malnutrition and wasting.

The drug of choice for therapy is TMP-SMX. Dosing options include 160mg TMP plus 800mg SMX administered four times a day for ten days or 320mg TMP plus 1,600mg SMX administered twice a day for ten to fourteen days. Treatment results in clearance of parasites, decrease in the volume of diarrhoea, and decreased abdominal pain within a mean of two and a half days after initiation of therapy.

No alternative treatment with proven efficacy exists for patients unable to tolerate sulfonamides, but the following agents have been used with anecdotal success:

- ❖ Pyrimethamine in doses of 50 to 75mg daily appears comparable to treatment with TMP-SMX. Folinic acid (5 to 10mg daily) should also be given to prevent bone marrow suppression.
- ❖ Ciprofloxacin and other fluoroquinolones have demonstrated activity against other *Apicomplexa* in animal studies and may represent second-line alternatives for treatment of isosporiasis. In a small, randomised clinical trial comparing ciprofloxacin with TMP and SMX in HIV-infected patients with isosporiasis, all treated with TMP-SMX cleared the organism and had cessation of diarrhoea within a median of two days, while ciprofloxacin was effective in 83% of patients with a median time to cessation of diarrhoea of four and a half days.<sup>vii</sup>
- ❖ Macrolide antibiotics have marginal efficacy in treating *I. belli* enteritis. Spiramycin (1.5g twice daily) and roxithromycin (2.5mg/kg every twelve hours) have been effective in a small number of patients with AIDS and chronic refractory isosporiasis.

Diclazuril (200 to 300mg daily for seven days), nitazoxanide (500mg twice daily for seven to ten days), and albendazole coupled with ornidazole were effective in small numbers of patients with AIDS and *I. belli* diarrhoea, and may be tried in patients intolerant of (or unresponsive to) TMP and SMX.

- ❖ Treatment with other anti-protozoal agents such as metronidazole, tinidazole, quinacrine, and furazolidone are probably of little value and are not recommended.
- ❖ Immune restoration following initiation of HAART in patients with AIDS is associated with more rapid resolution of symptoms and fewer relapses. HAART is therefore recommended as part of the treatment for patients with isosporiasis.

### ***Management of Treatment Failure***

Treatment failure is defined as persistence or worsening of diarrhoea and systemic symptoms after five to seven days of appropriate treatment. Re-treatment with a second-line alternative agent may result in improvement in those who fail initial therapy.

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

Infections tend to be chronic and relapsing, particularly in patients with AIDS and advanced immunosuppression. Treatment is usually effective in controlling symptoms but recurrences are common after treatment is stopped. This is most likely because the agents used to treat the infection are not active against the extra-intestinal tissue cyst stage of the parasite.

Patients with CD4+ T cell counts of  $<200$  cells/mm<sup>3</sup> should receive secondary prophylaxis with TMP (320mg) and SMX (1,600mg) once daily or three times a week. Pyrimethamine, 25mg daily, has also been used successfully for secondary prophylaxis following primary isosporiasis. Although not evaluated in any clinical trial or observational cohort setting, it is likely, as with other similar OIs, that secondary prophylaxis can be safely discontinued after an increase in CD4+ T cell counts to levels of  $>200$  cells/mm<sup>3</sup> sustained for at least three to six months following initiation of HAART.

### ***Special Considerations in Pregnancy***

The incidence, clinical manifestations, and course of *I. belli* infection do not appear to differ with pregnancy. Diagnosis and therapy should be the same as in non-pregnant adults.

## **CYCLOSPORA**

### ***Epidemiology***

*Cyclospora* cayetanensis has been implicated in outbreaks of diarrhoeal illness around the world and appears to be common in the Caribbean. A study of HIV-infected patients in Haiti revealed that over 10% of HIV-infected adults with diarrhoea in Haiti were infected with *Cyclospora*.<sup>viii</sup> Infection occurs via the faecal-oral route, and outbreaks attributable to contaminated water, fruits, and vegetables have been documented.

### ***Clinical Manifestations***

Signs and symptoms resemble those associated with *Cryptosporidium* and *Isospora* infections. Nausea, vomiting, anorexia, cramping abdominal pain, fever, malaise, and diarrhoea are common, though some patients may experience constipation as well. Unlike immunocompetent patients in whom the illness is self-limited, immunocompromised patients, such as those with AIDS, may experience severe and chronic infections. The small intestine is the primary site of infection.

### ***Diagnosis***

Microscopic examination of the stool can establish the diagnosis, though shedding of *Cyclospora* may be intermittent. *Cyclospora* oocysts may be seen with acid-fast staining of stool specimens, and resemble *Cryptosporidium* oocysts in shape but are roughly twice as large. Autofluorescence using epifluorescence microscopy can also establish the diagnosis.

### ***Treatment Recommendations and Management of Treatment Failure***

Supportive therapy includes fluid support if dehydration has developed and nutritional supplementation for malnutrition and wasting. TMP-SMX (320mg TMP plus 1,600mg SMX) twice a day for seven to ten days is generally effective; alternatively, ciprofloxacin 500mg twice a day for ten days may be used for patients who fail initial therapy with TMP-SMX or are intolerant of this agent. A small clinical trial in Haiti involving patients with diarrhoea due to *Cyclospora* or *Isospora* found that a seven-day course of TMP-SMX resulted in clinical cure in 100% of treated patients, while a seven-day course of ciprofloxacin was nearly as effective.<sup>ix</sup>

#### **Prevention of Recurrence**

TMP-SMX (320mg TMP plus 1,600mg SMX) once daily or ciprofloxacin 500mg daily can be used for secondary prophylaxis. Effective reconstitution of the immune system with HAART will also reduce susceptibility to *Cyclospora*.

#### **Special Considerations in Pregnancy**

Diagnosis and therapy should be the same as in non-pregnant adults.

## **MICROSPORIDIOSIS**

### **Epidemiology**

The *Microsporidia* reported as pathogens in humans include *Encephalitozoon cuniculi*, *E. hellem*, *E. (Septata) intestinalis*, *Enterocytozoon bieneusi*, *Trachipleistophora hominis*, *T. anthropophthera*, *Pleistophora species*, *P. ronneefyi*, *Vittaforma (Nosema) corneae*, *Microsporidium sp.*, *Nosema ocularum*, *Brachiola (Nosema) connori*, *B. vesiculatum*, and *B. (Nosema) algerae*.

In the pre-HAART era, reported prevalence rates of microsporidiosis varied between 2% and 70% in HIV-infected patients with diarrhoea, depending on the diagnostic techniques employed and the patient population described. The incidence of microsporidiosis has declined dramatically with the widespread use of effective HAART.

In the immunosuppressed host, microsporidiosis is most commonly seen when the CD4+ T cell count is <100 cells/mm<sup>3</sup>.

### **Clinical Manifestations**

The most common manifestation of microsporidiosis is gastrointestinal tract infection with diarrhoea; however, encephalitis, ocular infection, sinusitis, myositis, and disseminated infection are also described.

Clinical syndromes may vary with the infecting species. *E. bieneusi* is associated with malabsorption, diarrhoea, and cholangitis. *E. cuniculi* is associated with hepatitis, encephalitis, and disseminated disease. *E. (Septata) intestinalis* is associated with diarrhoea, disseminated infection, and superficial keratoconjunctivitis. *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, and disseminated infection. *Nosema*, *Vittaforma*, and *Microsporidium* are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Brachiola*, and *Trachipleistophora* are associated with myositis. *Trachipleistophora* is associated with encephalitis and disseminated disease.

### **Diagnosis**

Although microsporidia belonging to the genera *Encephalitozoon*, *Brachiola (B. algerae)*, *Vittaforma (V. corneae)*, and *Trachipleistophora* have been cultivated *in vitro*; *E. bieneusi* has not been successfully cultivated *in vitro*. In biopsy specimens, microsporidia can be visualised with Giemsa, Brown-Hopps gram stain, acid-fast staining, Warthin-Starry silver staining, haematoxylin and eosin, or Chromotrope 2A.

In gastrointestinal disease, examination of three stools with chromotrope and chemofluorescent stains is often sufficient for diagnosis. If stool examination is negative and microsporidiosis is

suspected, a small bowel biopsy should be performed. If the aetiological agent is *Encephalitozoonidae* or *Trachipleistophora*, examination of urine often reveals the organism.

### **Treatment Recommendations**

HAART with immune restoration (an increase of CD4+ T cell count to  $>100$  cells/mm<sup>3</sup>) is associated with resolution of symptoms of enteric microsporidiosis including those due to *E. bienuesi*. All patients should be offered HAART as part of the initial management of their infection. Nevertheless, available data suggest that microsporidia are suppressed but not eliminated by immune restoration.

Albendazole, a benzimidazole that binds to  $\beta$ -tubulin, has activity against many species of microsporidia, but it is not effective for *Enterocytozoon* infections. Fumagillin, a water-insoluble antibiotic made by *Aspergillus fumigatus*, also has activity *in vitro* and *in vivo*. Albendazole is recommended for initial therapy of intestinal and disseminated (not ocular) microsporidiosis due to microsporidia other than *E. bienuesi*.

Itraconazole may also be useful in disseminated disease when combined with albendazole, especially in infections due to *Trachipleistophora* or *Brachiola*. Ocular infections due to microsporidia should be treated topically with Fumidil B<sup>®</sup> (fumagillin bicyclohexylammonium) in saline (to achieve a concentration of 70 $\mu$ g/mL of fumagillin). Metronidazole and atovaquone are not active *in vitro* or in animal models and should not be used to treat microsporidiosis. Fluid support should be offered if diarrhoea has resulted in dehydration. Malnutrition and wasting should be treated with nutritional supplementation.

### **Monitoring and Adverse Events**

Albendazole side effects are rare but hypersensitivity (rash, pruritis, fever), neutropaenia (reversible), CNS effects (dizziness, headache), gastrointestinal disturbances (abdominal pain, diarrhoea, nausea, vomiting), hair loss (reversible), and elevated hepatic enzymes (reversible) have been reported. Albendazole is not carcinogenic or mutagenic. Topical fumagillin has not been associated with significant side effects. Oral fumagillin has been associated with thrombocytopaenia, which is reversible upon stopping the drug.

### **Management of Treatment Failure**

Optimising HAART to attempt to achieve full virologic suppression is currently the only feasible approach to management of patients who fail specific therapy.

### **Prevention of Recurrence**

Treatment for ocular microsporidiosis should be continued indefinitely as recurrence or relapse may follow treatment discontinuation. It is not known if treatment can be safely discontinued following immune restoration with HAART, although it is reasonable, based on the experience with discontinuation of secondary prophylaxis for other OIs during advanced HIV disease, to discontinue chronic maintenance therapy if patients remain asymptomatic with regard to signs and symptoms of microsporidiosis, and have a sustained (e.g. six months or longer) increase in their CD4+ T cell counts to levels  $>200$  cells/mm<sup>3</sup> after HAART.

### **Special Considerations in Pregnancy**

In animals (rats and rabbits), albendazole is embryotoxic and teratogenic at dosages of 30mg/kg. Thus, albendazole is not recommended for use in pregnant women. However, well-controlled studies in human pregnancy have not been performed.

Systemic fumagillin has been associated with increased resorption and growth retardation in rats. No data on use in human pregnancy are available. However, given the known anti-angiogenic effect of fumagillin, this drug should not be used in pregnant women. Topical fumagillin has not been associated with embryotoxic or teratogenic effects in pregnant women, and may be considered when therapy with this agent is appropriate.

## MYCOBACTERIUM TUBERCULOSIS (TB)

### *Epidemiology*

The World Health Organisation (WHO) estimates that TB is the cause of death for 11% of all AIDS patients in the world and has developed policy guidelines to rapidly scale up a collaborative approach to fight TB and HIV<sup>x</sup> through expansion of voluntary counselling and testing for HIV in TB programmes, intensified TB case-finding in HIV-infected patients, and other measures. These actions will be especially important in parts of the Caribbean where the overall HIV seroprevalence rates among patients with TB have been quite high. Although declining rates were seen in the Bahamas and in Trinidad & Tobago during the late 1990s, increasing rates were witnessed in Guyana and Suriname. There are currently 30% to 40% HIV seroprevalence rates among TB patients in Guyana, Trinidad, Tobago, and the Bahamas. TB has also been a common AIDS-defining illness in a number of other Caribbean countries.<sup>xi</sup>

TB occurs in HIV-infected persons at all CD4<sup>+</sup> T cell count levels. The clinical manifestations may be altered depending on the degree of immunosuppression. Those with more advanced immunosuppression (CD4<sup>+</sup> T cell counts of <200 cells/mm<sup>3</sup>) are more likely to have extrapulmonary or disseminated disease. In areas where TB is endemic, many patients have higher CD4<sup>+</sup> T cell counts at the time HIV-related TB develops.

TB in persons with HIV infection can develop immediately after exposure (primary disease) or as a result of progression following establishment of latent TB infection (LTBI), sometimes called *re-activation disease*. Primary TB has been reported in a number of outbreaks—frequently in individuals with advanced immune suppression—and may account for one-third or more of cases of TB in the HIV-infected population.

Progression to disease among those with latent TB infection has been dramatically more likely in HIV-infected persons than in HIV-uninfected persons in the Caribbean.<sup>xii</sup> HIV-uninfected persons with a positive tuberculin skin test (TST) result have a 5% to 10% lifetime risk of developing TB, compared with a 7% to 10% yearly risk in HIV-infected persons with a positive TST result.<sup>xiii</sup> Patients with TB have been shown to have higher HIV viral loads and a more rapid progression of their HIV illness than comparable HIV-infected patients without TB.

### *Clinical Manifestations*

With CD4<sup>+</sup> T cell counts of >350 cells/mm<sup>3</sup>, HIV-related TB presents like TB among HIV-uninfected persons. Most patients have the disease limited to the lungs, and common chest radiographic manifestations include upper lobe fibronodular infiltrates with or without cavitation. However, extrapulmonary disease is more common in HIV-infected individuals than in non-HIV-infected persons. When extrapulmonary disease does occur in HIV-infected persons, clinical manifestations are not substantially different from those described in HIV-uninfected patients.

With increasing immunodeficiency, extrapulmonary TB—with or without pulmonary involvement—becomes increasingly common. At CD4<sup>+</sup> T cell counts of <50 cells/mm<sup>3</sup>, extrapulmonary involvement (pleuritis, pericarditis, and meningitis) is common.

Among severely immunocompromised patients, TB can be a critical systemic disease with high fevers, rapid progression, and sepsis syndrome. The chest radiographic findings of TB in advanced AIDS patients are markedly different, however, than those among patients with less severe HIV infection. Lower lobe, middle lobe, and miliary infiltrates become common with advancing immunodeficiency, and cavitation becomes uncommon. Finally, patients with HIV infection and pulmonary TB can have sputum smears and culture results of positive for AFB or *M. tuberculosis* respectively, even with a normal chest radiograph.

Histopathological findings are affected by the degree of immunodeficiency. Patients with relatively intact immune function have typical granulomatous inflammation associated with

TB. With progressive immunodeficiency, granulomas become poorly formed or can be completely absent.

### **Diagnosis**

The evaluation of suspected HIV-related TB should always include a chest radiograph; pulmonary involvement is common at all stages of HIV disease. Sputum samples for AFB smear and culture should be obtained from patients with pulmonary symptoms, cervical adenopathy, or chest radiographic abnormalities. Sputum samples from a substantial fraction of cases of pulmonary TB are negative by direct smear microscopy. Nucleic-acid amplification (NAA) tests have been used as an adjunct to sputum smear and culture for rapid detection of *M. tuberculosis* in the French Caribbean.<sup>xiv</sup>

For patients with signs of extrapulmonary TB, needle aspiration of skin lesions, nodes, pleural, or pericardial fluid may allow for rapid diagnosis, culture, and susceptibility testing. Tissue biopsy can be helpful among patients with negative fine-needle aspirates. Among patients with signs of disseminated disease, mycobacterial blood cultures may allow a definitive diagnosis. mycobacterial blood cultures become increasingly sensitive for TB diagnosis among severely immunodeficient patients.

Among patients with relatively intact immune functions, the yield of sputum smear and culture exams is similar to that of HIV-uninfected adults, with positive smear results being more common among patients with cavitary pulmonary involvement. TST is positive in most patients with pulmonary disease and CD4+ T cell counts of >200 cells/mm<sup>3</sup>. Among patients with more severe immunodeficiency, sputum smear and culture exams become somewhat less sensitive, and TST has little diagnostic value because it is often negative. However, the yield of mycobacterial stain and culture of specimens from extrapulmonary sites (node aspirates, pleural and pericardial fluid) is higher among patients with advanced immunodeficiency compared to HIV-uninfected adults.

A positive smear result in any of these specimens (sputum, needle aspirate, tissue biopsy) represents some form of mycobacterial disease but does not always represent TB. However, because TB is the most virulent mycobacterial pathogen and can be spread from person to person if pulmonary involvement is present, patients with smear-positive results should be treated for TB until definitive mycobacterial species identification has been made.

Drug susceptibility testing and adjustment of the treatment regimen based on the results is recommended to ensure the successful treatment of TB and to prevent transmission of drug resistant *M. tuberculosis* in the community. Major outbreaks of multidrug resistant (MDR)-TB have so far occurred in HIV-infected patients in hospital and hospital clinic settings in the United States; Buenos Aires, Argentina; and Lima, Peru. Therefore, for all HIV-infected patients with TB, testing for susceptibility to first-line agents (isoniazid (INH), rifampin (RIF), rifabutin, or ethambutol (EMB)) should be performed wherever possible, regardless of the source of the specimen. Pyrazinamide (PZA) susceptibility testing should be performed on an initial isolate if there is a sufficiently high prevalence of PZA resistance in the community.

### **Treatment Recommendations**

Treatment of HIV-related TB should follow the general principles developed for TB treatment in the HIV-uninfected individual. Early diagnosis and treatment are critical. Because of the severity of TB among immunocompromised patients, directly observed therapy (DOT) is strongly recommended for patients with HIV-related TB. Multiple drugs and DOT are used to provide effective therapy, to prevent acquired drug resistance during treatment, and to allow a cure with a relatively short course of treatment (six to nine months).

HIV-infected patients have other social and medical needs and treatment success is enhanced by a case-management approach, which incorporates assistance with all of these needs (enhanced DOT) in addition to providing DOT.

There are several special considerations in the treatment of HIV-associated TB:

- Treatment is very effective, but the optimal duration of treatment is uncertain.
- Acquired drug resistance is unusual with the use of DOT, but does occur in HIV-infected persons.
- The risk of acquired rifamycin resistance has led to specific recommendations regarding dosing frequency (see below).
- The use of HAART among patients being treated for TB is complicated by overlapping drug toxicity profiles, drug-drug interactions, and an increase in TB manifestations during immune reconstitution (paradoxical reactions). Recent studies suggest that with careful attention to these complicating factors, the prognosis of HIV-related TB can be markedly improved with the provision of HAART, although the optimal relative timing between anti-TB and HIV therapy is uncertain.

Treatment of drug-susceptible TB in HIV-infected adults should include the use of a six-month regimen consisting of an initial phase of INH, RIF or rifabutin, PZA, and EMB given for two months followed by INH and RIF for four months, when the disease is caused by organisms known or presumed to be susceptible to first-line anti-TB drugs. Once the organism is shown to be susceptible to INH, RIF, and PZA, then EMB should be discontinued.

The optimal duration of therapy for HIV-related TB remains controversial. Studies in several developing countries have shown that patients with HIV-related TB respond well to standard six-month treatment regimens, with rates of treatment failure and relapse similar to those of HIV-uninfected patients. Concerns remain, though, that these results may not be applicable to patients with advanced HIV disease and TB. While awaiting definitive randomised comparisons in HIV-infected patients with TB, six months of therapy is probably adequate for most cases, but prolonged therapy (up to nine months) is recommended (as in HIV-negative patients) for patients with a delayed clinical or bacteriological response to therapy (symptomatic or positive culture results at or after two months of therapy, respectively) or perhaps with cavitary disease on chest radiograph.

Intermittent dosing (twice- or thrice-weekly) facilitates DOT by decreasing the total number of encounters required between the patient and the provider, making observed therapy more practical to deliver. However, once- or twice-weekly dosing has been associated with an increased rate of acquired rifamycin resistance among patients with advanced HIV disease (CD4+ T cell counts of  $<100$  cells/mm<sup>3</sup>). Acquired rifamycin resistance was relatively common with once-weekly rifapentine plus INH and also occurred in trials of twice-weekly rifabutin plus INH and twice-weekly RIF plus INH. Therefore, once-weekly rifapentine is contra-indicated in HIV-infected patients, and it is recommended that RIF- and rifabutin-based regimens be given at least three times weekly for patients with TB and advanced HIV disease (CD4+ T cell counts of  $<100$  cells/mm<sup>3</sup>). Although treatment approaches to this population need to be further evaluated in prospective trials, a prudent management strategy consists of daily DOT during the first two months of therapy and thrice-weekly DOT during the continuation phase of anti-TB therapy.

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

Close follow-up, consisting of clinical, bacteriological, and occasionally, laboratory and radiographic evaluations, is essential to ensure treatment success. In patients with pulmonary TB, at least one sputum specimen for microscopic examination and culture should be obtained at monthly intervals until two consecutive specimens are negative on culture. Drug susceptibility tests should be performed on isolates from patients who have positive cultures after three months of treatment. Patients who have positive cultures after four months of treatment should be considered as having failed therapy and be managed accordingly. For patients with extrapulmonary TB, the frequency and types of evaluations will depend on the sites involved and the ease with which specimens can be obtained.

A detailed clinical assessment should be performed at least monthly in order to identify

possible medication intolerance and to assess adherence. As a routine, it is not necessary to monitor blood tests for patients being treated with first-line drugs unless baseline abnormalities were identified. More frequent clinical and laboratory monitoring is indicated for patients with underlying liver disease, including hepatitis C co-infection, who are being treated for TB.

INH, RIF, and PZA all can cause drug-induced hepatitis, and the risk may be increased in patients taking other potentially hepatotoxic agents or in persons with underlying liver dysfunction. However, because of the effectiveness of these drugs (particularly INH and RIF), they should be used, if at all possible, even in the presence of pre-existing liver disease. Frequent clinical and laboratory monitoring should be performed to detect any exacerbation of hepatitis.

In general, independent of HIV status for all patients with TB, several treatment options exist if serum aminotransaminases are more than three times the upper limit of normal prior to the initiation of treatment (and the abnormalities are not thought to be caused by TB). One option is to use standard therapy with frequent monitoring. A second option is to treat with RIF, EMB, and PZA for six months, avoiding INH. A third option is to treat with INH and RIF for nine months, supplemented by EMB for the first two months, thereby avoiding PZA. For patients with severe liver disease, a regimen with only one hepatotoxic agent, generally RIF plus EMB, could be given for twelve months, preferably with another agent, such as a fluoroquinolone, for the first two months. As previously indicated, treatment may need to be lengthened for patients who are HIV-infected. For patients who develop worsening hepatic function on treatment, an expert should be consulted.

Tests to monitor hepatotoxicity (aminotransferases, bilirubin, alkaline phosphatase), renal function (serum creatinine), and platelet count should be obtained for all patients started on treatment for TB. At each monthly visit, patients taking EMB should be questioned regarding possible visual disturbances including blurred vision or scotomata; monthly testing of visual acuity and colour discrimination is recommended for patients taking doses that on a milligram per kilogram basis are greater than those listed in recommended doses and for patients receiving the drug for longer than two months.

Patients who have TB caused by strains of *M. tuberculosis* resistant to at least INH and RIF are at high risk for treatment failure and for further acquired drug resistance. Such patients should be referred to or have consultation obtained from specialised treatment centres. Although patients with strains resistant to RIF alone have a better prognosis than patients with MDR strains, they are also at increased risk for treatment failure and for developing additional resistance and should be managed in consultation with an expert.

### ***HAART in the Management of TB and Paradoxical Reactions***

Rifamycin drugs are essential components of short-course regimens for the treatment of TB. However, substantial adverse pharmacologic interactions occur between rifamycins and commonly-used ARV drugs, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), as a consequence of changes in drug metabolism resulting from induction or inhibition of the hepatic cytochrome P-450 (CYP450) enzyme system (see *Appendix E*). Of the available rifamycins, RIF is the most potent CYP450 inducer, and rifabutin has substantially less inducing activity. Despite such interactions, rifamycin should generally not be excluded from the TB treatment regimen in patients receiving HAART except in unusual circumstances.

**Table 1: Recommended Dose Adjustments When Patients Are Administered Rifabutin Concurrently with ARVs**

ARV REGIMEN	RIFABUTIN DOSE*	ARV DOSE ADJUSTMENT
<b>PI Regimens</b>		
Nelfinavir (NFV), indinavir (IDV), or	Decrease daily dose to	NFV: use 1,250mg q12h

amprenavir (APV) (+ 2 NRTIs)	150mg; use 300mg t.i.w	IDV: consider increase to 1,000mg q8h APV: no change
Ritonavir (RTV) (+ 2 NRTIs, other PIs, and/or NNRTIs)	Decrease to 150mg b.i.w or t.i.w <sup>†</sup>	None
Lopinavir (LPV) (+ 2 NRTIs and/or a NNRTI)	Decrease to 150mg b.i.w or t.i.w <sup>†</sup>	None
<b>NNRTI Regimens</b>		
Efavirenz (EFV) (+ 2 NRTIs)	Increase to 450mg q.d or 600mg b.i.w or t.i.w	None
Nevirapine (NVP) (+ 2 NRTIs)	300mg q.d or t.i.w	None
<b>NRTI Regimens</b>		
Dual or triple (e.g. zidovudine (AZT), lamivudine (3TC), and abacavir (ABC))**	300mg q.d or t.i.w	None
<b>PI + NNRTI Regimens</b>		
EFV or NVP + PI (except RTV, see above)	300mg q.d or t.i.w	Consider increased dose of IDV to 1,000mg q8h

\*Avoid twice-weekly rifabutin therapy among patients with CD4+ T cell counts of <100 cells/mm<sup>3</sup> at the time of TB diagnosis.

<sup>†</sup>When the dose of rifabutin is decreased, it is important to monitor adherence with RTV, because discontinuation of RTV may result in underdosing with rifabutin.

\*\*RIF increases concentrations of AZT and probably ABC. While the clinical significance of these changes is not clear, it is prudent to use rifabutin with triple NRTIs.

Either RIF or rifabutin can be used with NRTIs.<sup>1</sup> Rifabutin can be used with certain PIs or NNRTIs (other than delavirdine (DLV)) and has fewer problematic drug interactions than RIF. Adjustments in rifabutin or elements of the HAART regimen may be necessary with certain combinations (see *Table 1*). Two ARV drug regimens have been associated with a favourable outcome when administered with RIF: 1) EFV (potentially using an increased dose of 800mg daily) plus two NRTIs, and 2) RTV (600mg twice daily) plus two NRTIs. Serum concentrations of NVP may be adequate even in the presence of concentrations of RIF associated with enzyme induction, but clinical data are lacking. RIF should not be used with NFV, saquinavir (SQV), IDV, APV, atazanavir (ATV), or dual PI combinations using low-dose RTV (≤200mg twice daily) for which dosing guidelines are not available (see *Table 2*). In 2004, the CDC provided updated guidelines for the use of rifamycins in the treatment of TB in HIV-infected patients taking PIs or NNRTIs.<sup>xv</sup>

**Table 2: ARV-Anti-Infective Drug Combinations That Should Be Avoided**

FIRST DRUG	SECOND DRUG	REASON
Rifabutin	Atovaquone	Atovaquone conc. ↓ 34%; rifabutin conc. ↓ 19%
	Itraconazole	Itraconazole conc. ↓ 70%; potential for inhibition of rifabutin metabolism and ↑ rifabutin conc.

<sup>1</sup>In this chapter, the term "NRTI" encompasses both NsRTI (nucleoside reverse transcriptase inhibitor) and NtRTI (nucleotide reverse transcriptase inhibitor).

	SQV (as sole PI)	SQV AUC ↓ 43%; if used, consider addition of RTV and/or monitor SQV concentration; no change in rifabutin conc.
	Voriconazole	Voriconazole AUC ↓ 79%; rifabutin AUC ↑ 3-fold
RIF	APV	APV AUC ↓ 82%; Cmin ↓ 92%; no change in RIF conc.
	ATV	Pharmacokinetic study not available. Expect RIF to ↓ ATV concentrations substantially (up to 90%↓), as seen with other PIs
	Atovaquone	Atovaquone conc. ↓ 52%; RIF conc. ↑ 37%
	Clarithromycin	↓ mean clarithromycin conc. 87%
	DLV	DLV AUC ↓ 95%, no change in RIF conc.
	Fosamprenavir	No study done with fosamprenavir to date. APV AUC ↓ 82%; Cmin ↓ 92%
	IDV	IDV AUC ↓ 89%; RIF conc. slightly ↑
	Itraconazole	Itraconazole AUC ↓ 64-88%; no change in RIF conc.
	Ketoconazole	Ketoconazole levels ↓ 50%; RIF peak conc. ↓ 40%-50% probably due to impaired RIF oral absorption
	LPV/ritonavir (LPV/r)	LPV AUC ↓ 75% & Cmin ↓ 99%; ritonavir AUC may be increased
	NFV	NFV AUC ↓ 82%; no change in RIF conc.
	SQV (as sole PI)	SQV AUC ↓ 84%; no change in RIF conc.
	Voriconazole	Voriconazole AUC ↓ 96%

The optimal time for initiating HAART during TB treatment is not known. Because of the risk of prolonged airborne transmission of *M. Tuberculosis*, initiation of treatment for TB should never be delayed. Early initiation of HAART (within the first two to four weeks after the start of TB therapy) may decrease HIV disease progression, but may be associated with a relatively high incidence of side effects and paradoxical reactions (some severe enough to warrant discontinuation of both ARV and anti-TB drugs). Delaying the initiation of HAART for four to eight weeks after starting TB treatment has the potential advantages of being better able to ascribe a specific cause for a drug side effect, decreasing the severity of paradoxical reactions, and decreasing the adherence challenge for the patient. Until there have been controlled studies evaluating the optimal time for starting antiretroviral therapy in patients with HIV-associated TB, this decision should be individualised, based on the patient's initial response to TB therapy, occurrence of side effects, and acceptance of multidrug HAART. For these considerations, physicians should avoid beginning the simultaneous administration of both HAART and combination chemotherapy for TB; most experts would wait at least four to eight weeks.

Patients receiving HAART at the time treatment for TB is started require a careful assessment of the HAART regimen and, if necessary, changes to ensure optimum treatment of the HIV infection in the setting of TB therapy.

Because of the difficulties associated with the accurate diagnosis of an adverse drug reaction and in determining the responsible agent, the first-line anti-TB drugs should not be stopped

permanently without strong evidence that the anti-TB drug was the cause of the reaction. In such situations, consultation with an expert in treating TB in HIV-infected persons is recommended.

Patients may experience temporary exacerbation of symptoms, signs, or radiographic manifestations of TB after beginning anti-TB treatment. This phenomenon is termed a paradoxical (or immune reconstitution) reaction. This reaction occurs in non-HIV-infected persons, but it is more common among those with HIV infection, particularly those who receive HAART. These reactions presumably develop as a consequence of reconstitution of immune responsiveness brought about by HAART or perhaps by treatment of TB itself. Signs of a paradoxical reaction may include high fevers, increase in size and inflammation of involved lymph nodes, new lymphadenopathy, expanding CNS lesions, worsening of pulmonary parenchymal infiltrations, and increasing pleural effusions. Such findings should be attributed to a paradoxical reaction only after a thorough evaluation has excluded other possible causes, especially TB therapy failure.

A paradoxical reaction that is not severe should be treated symptomatically with NSAIDs, without a change in anti-TB therapy or HAART. Approaches to the management of severe reactions, such as high fever, airway compromise from enlarging lymph nodes, enlarging serosal fluid collections, and sepsis syndrome have not been studied. However, case reports have documented improvements with the use of prednisone or methylprednisolone used at a dose of approximately 1mg/kg and gradually reduced after one to two weeks.

#### ***Management of Drug Resistance and Treatment Failure***

If resistance to INH (with or without resistance to streptomycin) is detected, INH (and streptomycin, if used) should be discontinued and the patient treated with a six-month regimen of RIF, PZA, and EMB, which is nearly as effective as the conventional INH-containing regimen. Alternatively, treatment with RIF and EMB for twelve months may be used, preferably with PZA during at least the initial two months.

Treatment regimens for TB due to RIF mono-resistant strains are less effective, and patients infected with these strains are at increased risk of relapse and treatment failure. A minimum of twelve to eighteen months of treatment with INH, EMB, and a fluorquinolone (e.g. levofloxacin) with PZA given during the first two months is recommended. An injectable agent (e.g. amikacin or capreomycin) may be included in the first two to three months for patients with severe disease.

Patients with MDR-TB, defined as resistance to both INH and RIF, are at high risk of treatment failure and relapse and require especially close follow-up during (and often after) treatment. Treatment regimens for MDR-TB must be individualised, taking into account the resistance pattern, relative activities of available anti-TB agents, the extent of disease, and presence of co-morbid conditions. The management of MDR-TB is complex and should be undertaken only by an experienced specialist or in close consultation with specialised treatment centres.

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

Chronic suppressive therapy for patients who have successfully completed a recommended regimen of treatment for TB, as outlined above, is generally considered unnecessary. Re-infection, however, can occur. A study conducted in the late 1990s in Haiti<sup>xvi</sup> demonstrated that in HIV-infected persons completing treatment for active pulmonary TB, those assigned to post-treatment INH prophylaxis for one year had a significant reduction in recurrent TB during the twenty-four months after completing initial treatment, compared to those assigned to post-treatment placebo. Today, with increasing availability of HAART in the Caribbean, this approach might be considered most appropriate only for those with persistent immunosuppression despite use of HAART.

#### ***Special Considerations in Pregnancy***

HIV-infected pregnant women who lack documentation of negative TST results within the past year should be tested during pregnancy. The frequency of anergy is not increased during pregnancy, and routine anergy testing for HIV-infected pregnant women is not recommended. The diagnostic evaluation for TB in pregnant women is the same as for non-pregnant adults. Chest radiographs with abdominal shielding result in minimal foetal radiation exposure.

An increase in pregnancy complications, including preterm birth, low birth weight, and intrauterine growth retardation may be observed in pregnant women with both pulmonary and extrapulmonary TB not confined to the lymph nodes, especially when treatment is not begun until late in pregnancy.

In general, therapy of TB during pregnancy should be the same as for the non-pregnant adult but with attention given to the following considerations.

- INH is not teratogenic in animals or humans. Hepatotoxicity may occur more frequently in pregnancy and the postpartum period. Some experts recommend monthly monitoring of transaminases during pregnancy and the postpartum period.
- RIF is not teratogenic in humans. Because of a potential increased risk of RIF-related haemorrhagic disease in neonates born to women receiving anti-TB therapy during pregnancy, prophylactic vitamin K, 10mg, should be administered to the neonate.
- PZA is not teratogenic in animals. There is limited experience with use in human pregnancy. There are international recommendations by WHO and the International Union Against Tuberculosis and Lung Diseases for the routine use of PZA in pregnant women. If PZA is not included in the initial treatment regimen, the minimum duration of therapy should be nine months.
- EMB is teratogenic in rodents and rabbits at doses much higher than those used in humans. No teratogenicity has been observed in humans. Ocular toxicity has been reported in adults taking EMB, but changes in visual acuity have not been detected in infants born after exposure *in utero*.

Experience during pregnancy with most of the second-line drugs for TB is limited. MDR-TB in pregnancy should be managed in consultation with an expert; therapy should not be withheld because of pregnancy. The following issues should be considered when selecting second-line anti-TB drugs for use in pregnant women:

- Although no longer a first-line agent, streptomycin use has been associated with a 10% rate of VIII nerve toxicity in infants exposed *in utero*; its use during pregnancy should be avoided if possible.
- Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy *in utero*; like streptomycin, this agent should generally be avoided if possible. There is a theoretical risk of ototoxicity in the foetus with *in utero* exposure to amikacin and capreomycin, but this risk has not been documented, and these drugs may be alternatives when an aminoglycoside is required for treatment of MDR-TB.
- Because arthropathy has been noted in immature animals with the use of quinolones during pregnancy, quinolones are generally not recommended in pregnancy or in children age eighteen years or younger. However, more than 200 cases of ciprofloxacin use in pregnancy have been reported to various pregnancy registries, and its use has not been associated with arthropathy or birth defects after *in utero* exposure. Thus, quinolones may be used in pregnancy for drug resistant TB if required based on susceptibility testing.
- Para-aminosalicylic acid (PAS) has been associated with occipital bone defects when administered during pregnancy to rats. PAS is not teratogenic in rats or rabbits. A possible increase in limb and ear anomalies was reported among 143 pregnancies

with first-trimester exposure in one study. No specific pattern of defects and no increase in rate of defects have been detected in other human studies, suggesting that this agent may be used with caution if needed.

- Ethionamide has been associated with an increased risk of several anomalies in mice, rats, and rabbits following high-dose exposure; no increased risk of defects was noted with doses similar to those used in humans, but there is very limited experience with use in human pregnancy.
- There are no data available from animal studies or reports of cycloserine use in humans during pregnancy.

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

### ***Epidemiology***

Organisms of MAC are ubiquitous in the environment, and disseminated MAC infection has been clearly documented among HIV-infected patients in the Caribbean.<sup>xvii</sup> MAC infection is thought to be acquired through inhalation, ingestion, or inoculation via respiratory or gastrointestinal tract portals of entry. Household or close contacts of those with MAC disease are not at increased risk of developing the disease.

In the absence of effective HAART or chemoprophylaxis in those with advanced immunosuppression, the incidence of disseminated MAC disease in persons with AIDS ranges from 20% to 40%. Most cases of MAC disease occur in individuals with CD4+ T cell counts of  $<50$  cells/mm<sup>3</sup>. Other factors associated with increased susceptibility to MAC disease are high plasma HIV RNA levels ( $>100,000$  copies/mL), prior OIs (particularly CMV disease), and/or prior colonisation of the respiratory or gastrointestinal tract with MAC.

### ***Clinical Manifestations***

MAC disease in patients with AIDS, in the absence of antiretroviral therapy, is generally a disseminated multi-organ infection. Early symptoms may be minimal and may precede detectable intermittent or continuous mycobacteraemia by several weeks. Symptoms include fever, night sweats, weight loss, fatigue, diarrhoea, and abdominal pain.

Inflammatory IRS, characterised by focal lymphadenitis with fever, is a systemic inflammatory response with signs and symptoms clinically indistinguishable from active infection, and is similar to paradoxical reactions observed with TB. Bacteraemia is absent. The syndrome has been described in patients with subclinical or established MAC disease and advanced immunosuppression who begin HAART and have a rapid and marked increase in CD4+ T cell counts (of  $\geq 100$  cells/mm<sup>3</sup>). This syndrome may be benign and self-limited, or may be severe and require systemic anti-inflammatory therapy to alleviate clinical symptoms.

Other localised manifestations of MAC disease have been reported most commonly among those who are receiving and who have responded to HAART. Localised syndromes include cervical or mesenteric lymphadenitis, pneumonitis, pericarditis, osteomyelitis, skin or soft tissue abscesses, genital ulcers, or CNS infection.

Laboratory abnormalities particularly associated with disseminated MAC disease include anaemia (often out of proportion to that expected for stage of HIV disease) and elevated liver alkaline phosphatase. Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or, less commonly, peripheral) may be found on physical examination or by radiographic or other imaging studies. Other focal physical findings or laboratory abnormalities may occur in the context of those localised disease syndromes previously described.

### ***Diagnosis***

A confirmed diagnosis of disseminated MAC disease is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, bone marrow, or

other normally sterile tissue or body fluids.

Other ancillary studies provide supportive diagnostic information, including AFB smear and culture of stool or biopsy material obtained from tissues or organs, radiographic imaging of the abdomen or mediastinum for detection of lymphadenopathy, or other studies aimed at isolation of organisms from focal infection sites.

### ***Treatment Recommendations***

Initial treatment of MAC disease should consist of two antimycobacterial drugs to prevent or delay the emergence of resistance. Clarithromycin is the preferred first agent; it has been studied more extensively than azithromycin and appears to be associated with more rapid clearance of MAC from the blood. However, azithromycin may be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. EMB is the recommended second drug.

Some clinicians would add rifabutin as a third drug to improve survival and reduce emergence of drug resistance. The addition of rifabutin could be considered in individuals with advanced immunosuppression (CD4+ T cell counts of  $<50$  cells/mm<sup>3</sup>), high mycobacterial loads ( $>2$  log<sub>10</sub> colony forming  $\mu$ /mL of blood), or settings in which mortality is increased and emergence of drug resistance most likely. *Table 1* lists recommended dose adjustments when patients are administered rifabutin concurrently with ARV drugs. If rifabutin cannot be used due to drug interactions or intolerance, a third or fourth drug may be selected from among either the fluoroquinolones (ciprofloxacin or levofloxacin) or parenteral amikacin, although data supporting a survival or microbiologic benefit when these agents are added have not been compelling.

Patients diagnosed with disseminated MAC disease who have not previously received or are not currently receiving HAART should generally have HAART initiated simultaneously within one to two weeks of initiation of anti-mycobacterial therapy for MAC disease. If HAART has already been instituted, it should be continued and optimised for patients with disseminated MAC disease, unless drug interactions preclude the safe concomitant use of ARV and antimycobacterial drugs. For those who experience symptoms of moderate to severe intensity due to an inflammatory IRS in the setting of HAART, symptomatic treatment initially with NSAIDs is recommended. If symptoms fail to improve, short-term (four to eight weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40mg of oral prednisone once daily, have been successfully employed.

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

Adverse effects observed with clarithromycin and azithromycin consist of nausea, vomiting, abdominal pain, abnormal taste, and rarely elevations of liver transaminase levels or hypersensitivity reactions. Doses of clarithromycin in excess of 1g daily for treatment of disseminated MAC disease have been associated with increased mortality and should not be used. Adverse effects of rifabutin are described in the section on TB. Rifabutin doses of 450mg daily or higher have been associated with an increased of adverse drug interactions when used with clarithromycin or other drugs that inhibit cytochrome p450 isoenzyme 3A4, and may be associated with a higher risk of developing uveitis or other adverse drug reactions.

Improvement in fever and a decline in the quantity of mycobacteria in blood or tissue can be expected within two to four weeks after initiation of appropriate therapy. However, for those with more extensive disease or advanced immunosuppression, clinical response may be delayed. A repeat blood culture for MAC should be performed if possible on patients who fail to demonstrate clinical improvement (reduction in fever or systemic symptoms) within four to eight weeks of initiation of antimycobacterial therapy.

### ***Management of Treatment Failure***

Treatment failure is defined by the absence of a clinical response and the persistence of *Mycobacteremia* after four to eight weeks of treatment. Although the majority of patients

who failed clarithromycin- or azithromycin-primary prophylaxis in clinical trials had isolates susceptible to these drugs at the time MAC disease was detected, the number of drugs with demonstrated clinical activity against MAC is limited, and results of susceptibility testing should be used whenever possible to construct a new multidrug regimen consisting of at least two new drugs not previously used and to which the isolate is susceptible from among the following: EMB, rifabutin, ciprofloxacin or levofloxacin, or amikacin. It is not known whether continuing clarithromycin or azithromycin in the face of resistance provides additional benefit. Clofazimine should not be used based on the lack of efficacy demonstrated in randomised trials and the association with increased mortality.

For patients who have failed initial treatment for MAC disease, or who have antimycobacterial drug resistant MAC disease, optimising HAART is an important adjunct to second-line or salvage therapy for MAC disease.

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

Adult and adolescent patients with disseminated MAC disease should receive lifelong therapy (e.g. secondary prophylaxis or maintenance therapy), unless immune reconstitution occurs as a consequence of HAART. Apparently, patients are at low risk for recurrence of MAC when they have completed a course of twelve months or longer of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have a sustained increase (e.g. six months or longer) in their CD4+ T cell counts to >100 cells/mm<sup>3</sup> after HAART. Discontinuing chronic maintenance therapy among such patients is reasonable. Secondary prophylaxis should be reintroduced if the CD4+ T cell count decreases to <100 cells/mm<sup>3</sup>.

### ***Special Considerations in Pregnancy***

Indications for treatment are the same as in non-pregnant adults. Azithromycin is preferred over clarithromycin as the second agent with EMB or rifabutin due to the occurrence of birth defects in mice and rats associated with clarithromycin, not seen with azithromycin.

## ***BACTERIAL RESPIRATORY DISEASE***

### ***Epidemiology***

Bacterial pneumonia has been a common cause of HIV-related morbidity, especially in developing countries. In a study comparing rates among cohorts with similar risk factors for bacterial pneumonia, those with HIV infection were 7.8 times more likely to develop bacterial pneumonia than HIV-uninfected persons.

For many individuals, bacterial pneumonia is a presenting symptom of HIV disease. Studies have shown that patients can develop serious pneumococcal infections with relatively preserved CD4+ T cell counts.

The high rates of bacterial pneumonia and other pyogenic respiratory tract infections are likely due to multiple factors including qualitative B-cell defects that impair the ability to produce pathogen-specific antibodies; weakened neutrophil function or numbers or both; as well as non-HIV-related factors such as cigarette smoking, use of crack cocaine, IV drug use, alcoholism, or liver disease. The most consistent predictor of bacterial infections is the CD4+ T cell count.

The aetiology of bacterial pneumonia in patients with HIV infection has been reported in several studies. Consistent among these has been the relative prominence of *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. In most studies, the pathogens of atypical pneumonia (*Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*) are rarely encountered.

Based on data derived from studies of pneumococcal bacteraemia, infection with *S. pneumoniae* has been estimated to occur 150 to 300 times more commonly among patients with HIV infection than in age-matched HIV-uninfected populations. Recurrent pneumococcal pneumonia, either with the same or unrelated serotype, is also more common

among HIV-infected patients, with a rate of 8% to 25% within six months. Recent data suggest that re-infection with a different strain is more common than relapse.

In most series, *H. influenzae* (usually non-typable) is generally the second most common cause of bacterial pneumonia.

In patients with advanced immunosuppression, *S. aureus* and *P. aeruginosa* can cause particularly aggressive invasive pneumonias, sometimes associated with bacteraemia and frequent relapses after cessation of therapy.

As in pneumonia studies of HIV-uninfected patients, a high proportion (up to 33%) of patients with HIV infection will have no specific microbiologic aetiology defined. Importantly, many of these undefined cases are believed to be of possible bacterial aetiology.

### ***Clinical Manifestations***

HIV-infected patients with bacterial pneumonia generally present in a similar fashion to those without HIV infection. Lobar consolidation on chest radiograph is commonly seen and is a predictor of bacterial pneumonia, although atypical presentations with multilobar, nodular, or reticulonodular patterns are occasionally described. Patients ill over a period of weeks to months are more likely to have PCP, TB, or an endemic chronic fungal infection.

### ***Diagnosis***

The pace of the respiratory disease, the underlying CD4+ T cell count, the circulating neutrophil count, and the appearance of the infiltrate should guide the diagnostic evaluation for bacterial pneumonia. At a minimum, a chest radiograph, blood cultures, a white blood cell (WBC) count, and, if available, a Gram's stain and culture of an adequate expectorated sputum sample should be obtained prior to antibiotic administration if possible, though antibiotic administration should not be delayed more than thirty minutes after initial diagnosis of pneumonia. Since PCP is a common HIV-related respiratory infection and may co-exist with bacterial pneumonia, an induced sputum examination for *P. jiroveci* staining should be performed if there is a known CD4+ T cell count of  $<250$  cells/mm<sup>3</sup>, other sign of advanced immunodeficiency (such as thrush), a prior history of PCP or another AIDS-related condition, or diffuse infiltrates on CXR.

For both clinical and infection-control purposes, sputum samples (either expectorated or induced) for AFB staining and TB cultures should be obtained on all HIV-infected, hospitalised patients with pulmonary infiltrates in most Caribbean settings, especially where TB is common. A possible exception to this rule would be the patient who clearly has an acute onset of an illness consistent with bacterial pneumonia, has no exposure to TB, has a prior negative TST, and has not lived in or been exposed to high-prevalence areas for TB.

### ***Treatment Recommendations***

Therapy for HIV-related bacterial pneumonia should target the most commonly identified pathogens, in particular *S. pneumoniae* and *H. influenzae*. In general, treatment guidelines appropriate for HIV-uninfected patients are applicable to those with HIV infection as well. Specific recommended regimens include either an extended-spectrum cephalosporin (such as cefotaxime or ceftriaxone) or a fluoroquinolone with activity against *S. pneumoniae* (levofloxacin, moxifloxacin, or gatifloxacin).

Combination therapy with macrolide or quinolone plus a cephalosporin regimen should be considered in those with severe illness. It is important to determine whether or not meningitis is present, since the recommended fluoroquinolones do not reliably attain adequate cerebrospinal fluid (CSF) levels for treating pneumococcal meningitis. For patients with severe immunodeficiency (CD4+ T cell counts of  $<100$ /mm<sup>3</sup>), a known history of prior *Pseudomonas* infection, bronchiectasis, or relative or absolute neutropaenia, broadening empiric coverage to include *P. aeruginosa* and other gram-negative bacilli should be considered. Possible options for therapy would include ceftazidime, cefepime, piperacillin-tazobactam, a carbapenem, or high-dose ciprofloxacin or levofloxacin. For ceftazidime and ciprofloxacin, other antimicrobial agents would be needed to provide optimal coverage for

gram-positive infections.

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

A clinical response, defined by a reduction in fever and improvement in laboratory studies, physical findings, and respiratory symptoms, is generally seen within forty-eight to seventy-two hours following initiation of appropriate therapy. Radiographic improvement may require additional time.

### ***Management of Treatment Failure.***

HIV-infected patients who fail to respond to appropriate antimicrobial therapy, as determined by a lack of reduction in fever, failure of the total WBC to return toward normal, persistent or worsening pulmonary signs, symptoms or radiographic abnormalities, progressive hypoxaemia, or other evidence of progressive disease should undergo further evaluation to search for other infectious and non-infectious causes of pulmonary dysfunction. Broader spectrum antimicrobial therapy may be required while additional diagnostic testing is pursued. Management in consultation with an infectious disease expert is recommended.

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

The preventive strategy most effective against bacterial pneumonia in HIV-infected patients is the use of HAART. There is no well-documented benefit for maintenance therapy following successful completion of antibiotic treatment for bacterial respiratory tract infections. Adults and adolescents who have CD4+ T cell counts of  $\geq 200$  cells/mm<sup>3</sup> should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine if they have not received it during the previous five years. Yearly administration of influenza vaccine may be useful in preventing pneumococcal superinfection of influenza respiratory tract infections.

Administration of antibiotic chemoprophylaxis to HIV-infected patients who have frequent recurrences of serious bacterial respiratory infections may be considered. TMP-SMX, administered for PCP prophylaxis, and clarithromycin or azithromycin, administered for MAC prophylaxis, can prevent recurrent bacterial pneumonia caused by drug-sensitive organisms. However, using antibiotics solely for preventing the recurrence of serious bacterial respiratory infections carries the potential for development of drug resistant micro-organisms and drug toxicity.

### ***Special Considerations in Pregnancy***

The diagnosis of bacterial respiratory tract infections in pregnant women is the same as for non-pregnant adults, with appropriate shielding of the abdomen during radiographic procedures.

Clarithromycin should be avoided due to the occurrence of birth defects associated with its use in mice and rats. Because arthropathy has been observed in immature animals with the use of quinolones during pregnancy, quinolones are generally not recommended in pregnancy and in children age eighteen years or younger. However, quinolones may be used in pregnancy for drug resistant disease when other alternatives are not available.

Pneumococcal and influenza vaccines may be given during pregnancy, and influenza vaccine is recommended for all women who will be in the second or third trimester of pregnancy during the peak of influenza season. Since administration of vaccines may be associated with a transient rise in HIV RNA levels, vaccination of pregnant women is best done after HAART has been initiated to minimise increases in HIV RNA levels that may raise the risk of perinatal HIV transmission.

## ***BACTERIAL ENTERIC DISEASE***

### ***Epidemiology***

The three most common causes of bacterial diarrhoea in patients with HIV infection are *Salmonella*, *Campylobacter*, and *Shigella* species. Patients with HIV infection are at a markedly increased risk of developing salmonellosis.

*Campylobacter jejuni* has a reported incidence among HIV-infected individuals, particularly men who have sex with men (MSM), which is up to thirty-nine times higher compared with the general population.

Persons with HIV infection, particularly sexually active MSM, are at markedly increased risk of developing shigellosis. Data also suggest that *Shigella* bacteraemia is more common in HIV-infected persons and may occur in both mild and severe cases of clinical shigellosis. Relapses in gastroenteritis and bacteraemia after appropriate treatment have also been reported.

### ***Clinical Manifestations***

Three major clinical syndromes of salmonellosis have been described in patients with HIV infection: a) a self-limited gastroenteritis; b) a more severe and prolonged diarrhoeal disease associated with fever, bloody diarrhoea, and weight loss; and c) *Salmonella* septicaemia, which may present with or without gastrointestinal symptoms. Bacteraemia can occur with each of these syndromes and is more likely to occur in those with advanced immunosuppression. Since non-typhoidal *Salmonella* bacteraemia is rare in immunocompetent hosts, its diagnosis should prompt consideration of HIV testing. *Salmonella* bacteraemia in patients with AIDS has marked propensity for relapse. Early in the AIDS epidemic, the rate of recurrent bacteraemia was approximately 45% unless chronic suppressive therapy was given. *Campylobacter* disease in those with severe or progressive immunodeficiency is often associated with more prolonged diarrhoea, invasive disease, bacteraemia, and extraintestinal involvement. The development of antimicrobial resistance during therapy, often associated with clinical deterioration or relapse, also occurs more frequently among HIV-infected individuals.

Shigellosis in persons with HIV infection generally causes an acute, febrile, diarrhoeal illness with prominent upper and lower gastrointestinal symptoms. Bloody diarrhoea is more common with *Shigella* infection than with *Salmonella*.

### ***Diagnosis***

Bacterial enteric infection is diagnosed through cultures of stool and blood. Given the high rate of bacteraemia associated with *Salmonella* gastroenteritis—in particular in patients with advanced HIV disease—blood cultures should be obtained whenever possible in any HIV-infected patient presenting with diarrhoea and fever. Persons with HIV are also at risk for disease due to non-*jejuni* *Campylobacter* species, including *C. foetus*, *C. upsaliensis*, *C. laridis*, *C. cineadi*, and *C. fennelliae*. While blood culture systems will generally grow these organisms, routine stool cultures performed by most laboratories will fail to identify these more fastidious *Campylobacter* species. If a lower endoscopy is performed, ulcerations similar to those seen with CMV colitis may be evident and can only be distinguished through histopathologic examination and culture.

### ***Treatment Recommendations***

Immunocompetent hosts without HIV infection seldom require treatment for *Salmonella* gastroenteritis; the condition is self-limited and treatment may prolong the carrier state. With HIV infection, the risk of bacteraemia is sufficiently high that most experts recommend antimicrobial treatment of all HIV-associated *Salmonella* infections. The initial treatment of choice for *Salmonella* infection is a fluoroquinolone. Ciprofloxacin is the preferred agent. Other fluoroquinolones (levofloxacin, gatifloxacin, and moxifloxacin) would also likely be effective in treatment of salmonellosis in HIV-infected persons.

For HIV-related *Salmonella* infection presenting with mild gastroenteritis without bacteraemia, seven to fourteen days of treatment is reasonable in an effort to reduce the risk of extraintestinal spread. For patients with advanced HIV disease (CD4+ T cell counts of <200/mm<sup>3</sup>) and/or who have *Salmonella* bacteraemia, at least four to six weeks of treatment is recommended. Depending on antibiotic susceptibility, alternatives to the fluoroquinolone antibiotics for *Salmonella* infections include TMP-SMX or expanded spectrum cephalosporins, such as ceftriaxone or cefotaxime.

The optimal treatment of campylobacteriosis in persons with or without HIV infection is poorly defined. For mild disease, some clinicians might withhold therapy unless symptoms persist for more than several days. Rising resistance to fluoroquinolones makes the choice of therapy especially problematic. For mild to moderate disease, initiating therapy with a fluoroquinolone (ciprofloxacin) or a macrolide (azithromycin), pending susceptibility test results, and treating for seven days is a reasonable approach. Patients with bacteraemia should be treated for at least two weeks, and it may be prudent to add a second active agent, such as an aminoglycoside, in such cases.

Therapy of shigellosis is indicated both to shorten the duration of illness and to prevent the spread of the infection to others. The recommended treatment is with a fluoroquinolone for three to seven days. Alternatives include TMP-SMX for three to seven days or azithromycin for five days. *Shigella* acquired in the Caribbean has high rates of TMP-SMX resistance; as a result, fluoroquinolones are preferred as first-line treatments. Treatment of patients who have *Shigella* bacteraemia is less well-defined. Depending on the severity of infection, it may be reasonable to extend treatment to fourteen days using the agents described above.

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

Patients should be monitored closely for improvement in systemic signs and symptoms and resolution of diarrhoea. A follow-up stool culture to demonstrate clearance of the organism is not generally required if a complete clinical response has been demonstrated, but should be considered for those who fail to clinically respond to appropriate antimicrobial therapy or when public health considerations dictate the need to assure microbiologic cure (e.g. healthcare or food service workers).

#### ***Management of Treatment Failure***

Treatment failure is defined by the lack of improvement in clinical signs and symptoms of diarrhoeal illness coupled with the persistence of organisms in stool, blood, other relevant body fluids, or tissue after completion of appropriate antimicrobial therapy for the recommended duration. Many patients with *Salmonella* bacteraemia may remain febrile for five to seven days despite effective therapy. Therefore, careful observation is required to determine the adequacy of the response. Treatment is best guided by drug susceptibility testing of isolates recovered in culture. An evaluation of other factors that may contribute to failure or relapse, such as malabsorption of oral antibiotics, a sequestered focus of infection (such as an undrained abscess), or adverse drug reactions that interfere with antimicrobial activity, should be undertaken as indicated.

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

HIV-infected persons who have *Salmonella* bacteraemia should receive long-term therapy (e.g. secondary prophylaxis or chronic maintenance therapy) to prevent recurrence. Fluoroquinolones, primarily ciprofloxacin, are the drugs of choice for susceptible organisms. Chronic suppressive or maintenance therapy is not generally recommended for *Campylobacter* or *Shigella* infections in persons with HIV infection.

Household contacts of HIV-infected persons who have salmonellosis or shigellosis should be evaluated for persistent asymptomatic carriage of *Salmonella* or *Shigella* so that strict hygienic measures or antimicrobial therapy can be instituted and recurrent transmission back to the HIV-infected person can be prevented.

#### ***Special Considerations in Pregnancy***

Because arthropathy has been observed in immature animals with the use of quinolones during pregnancy, quinolones are generally not recommended in pregnancy and in children age eighteen years or younger. Therefore, expanded spectrum cephalosporins, TMP-SMX, or azithromycin, depending on the organism and the results of susceptibility testing, should generally be considered as first-line therapy. However, quinolones may be used in pregnancy for drug resistant disease. Neonatal care providers should be informed of maternal sulfa therapy if used near delivery due to the theoretical increased risk of hyperbilirubinemia and kernicterus to the newborn.

## **BARTONELLOSIS**

### ***Epidemiology***

Bacillary angiomatosis, first recognised in 1983, and associated illnesses such as peliosis hepatica, are caused by bacteria of the genus *Bartonella*, most commonly *Bartonella henselae* and *Bartonella quintana*. Cases of bacillary angiomatosis in patients with HIV/AIDS have been linked to cat exposure. It is seen in increased frequency in the homeless and under conditions of poor sanitation.

Bacillary angiomatosis occurs most frequently late in HIV infection in patients with a median CD4+ T cell count of  $<50$  cells/mm<sup>3</sup> and has been documented in an HIV-infected patient in Nassau (Orlander, personal communication). Bartonellosis is often a chronic illness with disease lasting for months to years in most patients.

### ***Clinical Manifestations***

*Bartonella* species have been associated with infections involving every organ system, but the characteristic presentation is bacillary angiomatosis of the skin. Bacillary angiomatosis resembles KS. Lesions are often papular, red, with smooth or eroded surfaces, vascular, and bleed if traumatised. Nodules may be seen in the subcutaneous tissue and can erode through the skin. Bone infection has been reported and such infections are notable in that they are lytic and painful. *Bartonella* infection of the liver produces hepatic bacillary peliosis characterised by vascular masses in the liver or spleen. Although isolated organ systems may be affected, infection results from haematogenous dissemination, and systemic symptoms of fever, sweats, fatigue, malaise, weight loss, and other symptoms may accompany localised syndromes.

### ***Diagnosis***

The diagnosis is confirmed by histopathologic examination of tissue biopsy specimens. Lesions produce vascular proliferative histopathology; modified Silver stain demonstrates numerous bacilli. Tissue Gram's stain or acid-fast staining are negative.

### ***Treatment Recommendations***

Erythromycin and doxycycline have been used successfully to treat bacillary angiomatosis, peliosis hepatica, bacteraemia, and osteomyelitis and are considered first-line treatment for bartonellosis based on reported experience in case series. The duration of therapy should be at least three months. Doxycycline is the treatment of choice for CNS bartonellosis. Clarithromycin or azithromycin have been associated with clinical response in some cases, and are considered second-line alternatives, although treatment failures have been reported with both drugs. Quinolones have variable *in vitro* activity and clinical response in case reports; they are not recommended as first-line therapy but may be tried as second-line alternatives.

### ***Management of Treatment Failure and Prevention of Recurrence***

For patients who fail to respond to initial treatment, one or more of the second-line alternative regimens should be considered. For patients who relapse, lifelong suppression of infection with erythromycin or doxycycline should be considered.

### ***Special Considerations in Pregnancy***

Pregnancy has been associated with a more severe course and possible increased risk of death with acute infection due to *B. bacilliformis* in immunocompetent patients. Similarly, *B. bacilliformis* infections during pregnancy may increase the risk of spontaneous abortion and stillbirth and may be transmitted to the foetus.

Treatment during pregnancy should be with erythromycin rather than tetracyclines due to increased hepatotoxicity and staining of foetal teeth and bones associated with tetracycline use during pregnancy. Cephalosporins are not recommended.

## ***SYPHILIS***

### ***Epidemiology***

Although the incidence of syphilis has declined since the mid- to late 1980s in the Caribbean region, the incidence remains relatively high in several Caribbean countries<sup>xviii</sup> where syphilis has been seen with increased incidence in HIV-infected individuals, sex workers, and MSM.<sup>xix</sup> HIV infection appears to alter the diagnosis, natural history, management, and outcome of *Treponema pallidum* infection.

### ***Clinical Manifestations***

As in HIV-uninfected individuals, primary syphilis commonly presents as a single, painless nodule at the site of contact that rapidly ulcerates to form a classic chancre; however, in HIV-infected persons, multiple or atypical chancres occur, and primary lesions may be absent or missed.

Progression to secondary syphilis generally follows in two to eight weeks after primary inoculation, and is a reflection of ongoing replication and dissemination of *T. pallidum* in the absence of an effective host immune response. Although more rapid progression to secondary syphilis or severe disease may be more common in HIV-infected persons with advanced immunosuppression than in immunocompetent persons, the clinical manifestations are, in general, similar to those in HIV-uninfected individuals. Secondary syphilis, and in particular, acute syphilitic meningitis, must be distinguished from acute primary HIV infection. Constitutional symptoms, along with non-focal CNS symptoms and CSF abnormalities (lymphocytic pleocytosis with a mildly elevated CSF protein), are common to both.

Some of the manifestations of neurologic complications or neurosyphilis progress more rapidly or occur earlier in the course of disease in persons with HIV infection, and thus are not truly “late” complications or manifestations. However, concomitant uveitis and meningitis may be more common in HIV-infected patients with syphilis.

### ***Diagnosis***

The diagnosis of syphilis depends on a variety of tests that either directly detect the organism (e.g. darkfield microscopy or Direct Fluorescent Antibody-*T. Pallidum* (DFA-TP)) or serum antibodies against it (e.g. FTA-ABS and TP-TA), or indirectly indicate the presumptive presence of *T. pallidum* by detecting non-treponemal antibodies generated during infection (e.g. VDRL and RPR). Concurrent HIV infection probably does not change the performance of standard tests for the diagnosis of syphilis.

In early-stage disease (primary, secondary, and early-latent syphilis), responses to non-treponemal serologic tests (i.e., VDRL and RPR) may be atypical (e.g. higher, lower, or delayed) in HIV-infected versus HIV-uninfected patients with early-stage syphilis, but treponemal tests do not perform differently in HIV-infected compared to HIV-uninfected patients.

By definition, patients presenting with latent syphilis have serological evidence of disease in the absence of clinical or other laboratory abnormalities (e.g. normal CSF profiles).

The diagnosis of neurosyphilis is established by examination of the CSF, which may show mild mononuclear pleocytosis (10-200 cells/mm<sup>3</sup>), normal or mildly elevated protein concentrations, or a reactive CSF-VDRL. The CSF-VDRL is specific but not sensitive, and a reactive test establishes the diagnosis of neurosyphilis but a non-reactive test does not exclude the diagnosis. In contrast, CSF treponemal tests, such as the CSF FTA-ABS, are sensitive but not specific, and a non-reactive test excludes the diagnosis of neurosyphilis, but a reactive test does not establish the diagnosis. A reactive CSF-VDRL and a CSF WBC of  $\geq 10$  cells/mm<sup>3</sup> support the diagnosis of neurosyphilis; most experts would not base the diagnosis solely on elevated CSF protein concentrations in the absence of these other abnormalities. HIV infection itself may be associated with mild mononuclear CSF pleocytosis (5 to 15 cells/mm<sup>3</sup>), particularly in individuals with peripheral blood CD4+ T cell counts of  $>500$

cells/mm<sup>3</sup>; thus, establishing the diagnosis of neurosyphilis may be more difficult in such individuals. If neurosyphilis cannot be excluded by a non-reactive CSF treponemal test, such individuals should be treated for neurosyphilis, despite the acknowledged uncertainty of the diagnosis.

### **Treatment Recommendations**

The management of HIV-infected patients with syphilis is similar to the management of HIV-uninfected persons with the disease (see *Table 3*). However, closer follow-up is recommended to detect potential treatment failures or disease progression.

**Table 3: Recommended Regimens for the Treatment of Syphilis in HIV-Infected Patients**

<b>Early-Stage:</b> (Primary, secondary, and early-latent)	Benzathine penicillin G, 2.4MU intramuscular (IM) x 1
<b>Late-Latent</b>	Benzathine penicillin G, 2.4MU IM q.w x 3 weeks
<b>Late-Stage:</b> (Aortitis and gummata)	Infectious diseases consultation
<b>Neurosyphilis:</b> (CNS and ocular)	Infectious diseases consultation  Crystalline penicillin G, 18-24MU q.d, administered 3-4MU IV q4h or by continuous infusion for 10-14 days  or  Procaine penicillin, 2.4MU IM q.d plus probenecid, 500mg orally q.i.d x 10-14 days  Each ±  Benzathine penicillin G, 2.4MU IM q.w x 3 weeks after completion of above

For all patients with syphilis, regardless of disease stage, those with neurological or ocular symptoms or signs should undergo CSF examination to rule out neurosyphilis. CSF examination is also recommended for HIV-infected patients with late-latent syphilis, including those with syphilis of unknown duration. Similar to the HIV-uninfected population, HIV-infected patients with active tertiary syphilis (aortitis and gumma) or who fail treatment for non-neurological syphilis should undergo CSF examination. Patients with CSF abnormalities consistent with neurosyphilis should be treated for neurosyphilis.

HIV-infected individuals with early-stage (primary, secondary, or early-latent) syphilis should receive a single IM injection of 2.4 million units of benzathine penicillin G. Alternative therapies, including oral doxycycline, ceftriaxone, and azithromycin have not been sufficiently evaluated in HIV-infected patients to warrant use as first-line treatment. If an alternative to penicillin is used, treatment must be undertaken with close clinical monitoring.

In HIV-infected patients with late-latent syphilis for whom the CSF examination excludes the diagnosis of neurosyphilis, treatment is recommended with three weekly IM injections of 2.4 million units benzathine penicillin G. Alternative therapy with doxycycline 100mg orally twice a day for twenty-eight days has not been sufficiently evaluated in HIV-infected patients to warrant use as first-line treatment. If an alternative to penicillin is used, treatment must be undertaken with close clinical monitoring.

HIV-infected patients with clinical or laboratory evidence of neurosyphilis (CNS involvement including otic and ocular disease, even with a normal CSF) should receive IV aqueous crystalline penicillin G, 18 to 24 million units daily, administered 3 to 4 million units IV every four hours or by continuous infusion for ten to fourteen days, or procaine penicillin 2.4

million units IM once daily plus probenecid 500mg orally four times a day for ten to fourteen days. HIV-infected patients allergic to sulfa-containing medications should not be given the IM alternative because they are very likely to be allergic to probenecid. IM procaine penicillin without probenecid does not achieve sufficient penicillin levels in CSF to treat neurosyphilis. Some experts recommend following neurosyphilis treatment with three weeks of benzathine penicillin, 2.4 million units IM weekly. For penicillin-allergic patients, penicillin desensitisation followed by one of the penicillin regimens listed above is the preferred approach. However, limited data suggest that ceftriaxone (2g daily IV for ten to fourteen days) may be an alternative regimen.

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

Clinical and serological responses to treatment of early-stage (primary, secondary, and early-latent) disease should be monitored at three, six, nine, twelve, and twenty-four months after therapy. Serological responses to treatment in HIV-infected patients may differ from responses in HIV-uninfected individuals, including temporal pattern of response and proportion of subjects achieving serologically-defined treatment success (at least a four-fold decrease in titer).

After successful treatment for syphilis in HIV-infected and HIV-uninfected patients, some remain *serofast*, meaning that serum non-treponemal test titers remain reactive at low and unchanging titers, generally  $\leq 1:8$ , for extended periods of time (up to the lifetime of the patient). The serofast state probably does not represent treatment failure. Serologic evidence of potential re-infection should be based on at least a four-fold increase in titer above the established serofast baseline.

Response to therapy of late-latent syphilis should be monitored using non-treponemal serologic tests at three, six, twelve, eighteen, and twenty-four months to assure at least a four-fold decline in titer.

Concomitant HIV infection may be associated with poorer CSF and serological responses to neurosyphilis therapy. Repeat CSF examination is recommended at three and six months after completion of therapy for neurosyphilis where possible, and then every six months until the CSF WBC is normal and the CSF-VDRL is non-reactive. Treatment should be undertaken in consultation with an expert, where possible.

#### ***Management of Treatment Failure***

Re-treatment of patients with early-stage syphilis should be considered for those who: 1) do not experience at least a four-fold decrease in serum non-treponemal test titers six to twelve months after therapy; 2) have a sustained four-fold increase in serum non-treponemal test titers after an initial reduction after treatment; or 3) have persistent or recurring clinical signs or symptoms of disease. If CSF examination does not confirm the diagnosis of neurosyphilis, such patients should receive 2.4 million units IM benzathine penicillin G administered at one-week intervals for three weeks. If titers fail to appropriately respond after re-treatment, repeat CSF evaluation or re-treatment may not be beneficial.

Patients with late-latent syphilis should have a repeat CSF examination and be retreated if they develop clinical signs or symptoms of syphilis, have a four-fold increase in serum non-treponemal test titer, or experience an inadequate serologic response (less than four-fold decline in non-treponemal test titer) within twelve to twenty-four months of therapy. If the CSF exam is consistent with CNS involvement, re-treatment should follow the neurosyphilis recommendations; those without a profile suggesting CNS disease should receive a repeat course of benzathine penicillin, 2.4 million units IM weekly for three weeks, although some experts recommend following the neurosyphilis recommendations in this setting.

Re-treatment of neurosyphilis should be considered if the CSF WBC count has not decreased after six months following completion of treatment, or if the CSF-VDRL remains reactive two years after treatment.

#### ***Special Considerations in Pregnancy***

All pregnant women should be screened for syphilis at the first prenatal visit. All women delivering a stillborn infant after twenty weeks of gestation should also be tested for syphilis. Syphilis screening should also be offered at sites providing episodic care to pregnant women at high risk including emergency departments, jails, and prisons. No infant should leave the hospital without documentation of maternal syphilis serology status during pregnancy. The rate of transmission and adverse outcomes of untreated syphilis are highest with primary, secondary, and early latent syphilis during pregnancy and decrease with increasing duration of infection thereafter. Concurrent syphilis infection may increase the risk of perinatal transmission of HIV to the infant although an increased risk has not been consistently reported.

Treatment during pregnancy should consist of the same penicillin regimen as recommended for the given disease stage in non-pregnant, HIV-infected adults. Given concerns regarding the efficacy of standard therapy in HIV-infected individuals, a second injection one week after the first for HIV-infected pregnant women should be considered.

No alternatives to penicillin have been proven effective and safe for treatment of syphilis during pregnancy or for prevention of foetal infection. Pregnant women who have a history of penicillin allergy are best referred for skin testing and desensitisation and treatment with penicillin. Erythromycin does not reliably cure foetal infection; tetracyclines should not be used during pregnancy because of hepatotoxicity and staining of foetal bones and teeth. Efficacy data with azithromycin or ceftriaxone are insufficient to support a recommendation for their use in this setting.

The Jarisch-Herxheimer reaction, associated with fever within hours after treatment, may precipitate preterm labour or foetal distress during the second-half of pregnancy. Consideration should be given to providing foetal and contraction monitoring for twenty-four hours after initiation of treatment for early syphilis of pregnant women who are at or beyond twenty weeks of gestation, especially in the setting of abnormal ultrasound findings indicative of foetal infection. Alternatively, women should be advised to seek obstetric attention after treatment if they notice contractions or a decrease in foetal movement.

Repeat serologic titers should be performed in the third trimester and at delivery for women treated for syphilis during pregnancy.

## ***MUCOCOETANEOUS CANDIDIASIS***

### ***Epidemiology***

Most oropharyngeal and oesophageal candidiasis is caused by *Candida albicans*. Fluconazole (or azole) resistance is predominantly the consequence of previous exposure to fluconazole (or other azoles), particularly with repeated and long-term exposure. With such exposure, *C. albicans* resistance has been accompanied by a gradual emergence of non-*albicans Candida* species, particularly *C. glabrata*, as a cause of refractory mucosal candidiasis, particularly in patients with advanced immunosuppression. Oesophageal candidiasis is a frequent presenting symptom of AIDS in the Caribbean.<sup>xx</sup>

Oropharyngeal and oesophageal candidiasis are recognised as indicators of immune suppression and are most often observed in patients with declining CD4+ T cell counts of >200 cells/mm<sup>3</sup>. In contrast, vulvovaginal candidiasis is common in healthy, adult women, and is unrelated to HIV status.

### ***Clinical Manifestations***

Oropharyngeal candidiasis is characterised by painless, creamy white, plaque-like lesions of the buccal or oropharyngeal mucosa or tongue surface. Lesions can be easily scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular chelosis is also noted on occasion and may be due to *Candida*.

Oesophageal candidiasis is occasionally asymptomatic but often presents with fever, retrosternal burning pain or discomfort, and odynophagia. Endoscopic examination reveals whitish plaques similar to those observed with oropharyngeal disease that may progress to superficial ulceration of the oesophageal mucosa, with central or surface whitish exudates.

Vulvovaginitis may be mild to moderate and sporadic, similar in presentation to that in normal hosts, and characterised by a creamy to yellow-white adherent vaginal discharge associated with mucosal burning and itching. In those with more advanced immunosuppression, episodes may be more severe, more frequently recurrent, of longer duration, or refractory to treatment.

### ***Diagnosis***

The diagnosis of oropharyngeal candidiasis is usually a clinical one based on the appearance of the lesions. The feature that distinguishes these from oral hairy leukoplakia is the ability to scrape off the superficial whitish plaques. Scraping for microscopic examination for yeast forms using a potassium hydroxide (KOH) preparation provides supportive diagnostic information. Cultures of clinical material identify the species of yeast present. The definitive diagnosis of oesophageal candidiasis requires endoscopic visualisation of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and culture confirmation of the presence of *Candida* species. Although symptoms of oesophageal candidiasis may be mimicked by other pathogens, a diagnostic trial of antifungal therapy is often appropriate before endoscopy is undertaken to search for other causes of oesophagitis. The diagnosis of vulvovaginal candidiasis is based on the demonstration of characteristic hyphae or pseudohyphae forms in vaginal secretions examined microscopically after KOH preparation. Culture confirmation is rarely required. As self-diagnosis of vulvovaginitis is unreliable, microscopic confirmation is required to avoid unnecessary exposure to inappropriate treatments.

### ***Treatment Recommendations***

Although initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches or nystatin suspension or pastilles, oral fluconazole is as effective and in some studies, superior to topical therapy and is more convenient and generally better tolerated. Itraconazole oral solution for seven to fourteen days is as effective as oral fluconazole but less well-tolerated. Ketoconazole and itraconazole capsules are less effective than only fluconazole due to their more variable absorption and should be considered second-line alternatives.

Systemic therapy is required for effective treatment of oesophageal candidiasis. A fourteen to twenty-one day course of either fluconazole or itraconazole solution is highly effective. As with oropharyngeal candidiasis, ketoconazole and itraconazole capsules are less effective than fluconazole because of variable absorption. Although caspofungin and voriconazole are effective in treating oesophageal candidiasis in HIV-infected patients, experience is limited and the expense is high. As such, fluconazole remains the preferred agent.

Vulvovaginal candidiasis in HIV-infected women is uncomplicated in 90% of cases and responds readily to short-course oral or topical treatment with any of the following therapies including single-dose regimens: topical azoles (clotrimazole, butoconazole, miconazole, ticonazole, or terconazole) for three to seven days; topical nystatin 100,000 $\mu$  daily for fourteen days; oral itraconazole 200mg twice daily for one day or 200mg once-daily oral solution for three days; or one dose of oral fluconazole. Complicated vaginitis (prolonged or refractory episodes) is seen in approximately 10% of cases and requires antimycotic therapy for more than seven days.

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

Most patients respond rapidly to adequate therapy, with improvement in signs and symptoms within forty-eight to seventy-two hours. Short courses of topical therapy rarely result in adverse effects, although occasional patients experience coetaneous hypersensitivity reactions with rash and pruritis. Patients may experience gastrointestinal upset with oral azole

treatment. Treatment for longer than seven to ten days with azoles orally may produce hepatotoxicity. If prolonged therapy is anticipated (more than twenty-one days), periodic monitoring of liver chemistry studies should be considered.

#### ***Management of Treatment Failure***

Treatment failure is generally defined as signs and symptoms of oropharyngeal or oesophageal candidiasis that persist for more than seven to fourteen days of appropriate therapy. Fluconazole-refractory oropharyngeal candidiasis will respond at least transiently to itraconazole solution in approximately two-thirds of individuals. Amphotericin B oral suspension (1 mL four times daily of the 100mg/mL suspension) is sometimes effective in patients with oropharyngeal candidiasis who do not respond to itraconazole. However, amphotericin B solution is not widely available. IV amphotericin B is usually effective and may be used in patients with refractory disease. Fluconazole-refractory oesophageal candidiasis should be treated with caspofungin or IV amphotericin B, either conventional, liposomal, or lipid complex formulations.

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

Most HIV specialists do not recommend chronic prophylaxis of recurrent oropharyngeal or vulvovaginal candidiasis. However, if recurrences are frequent or severe, an oral azole, fluconazole, or itraconazole solution (or for recurrent vulvovaginal candidiasis, daily prophylaxis with any topical azole) should be considered. Factors that influence choices related to such therapy include impact of recurrences on the patient's well-being and quality of life, the need for prophylaxis for other fungal infections, cost, toxicities, drug interactions, nutritional status, and potential to induce drug resistance among *Candida* and other fungi.

Prolonged use of systemically absorbed azoles, specifically among patients with low CD4+ T cell counts (<100 cells/mm<sup>3</sup>) increases the risk for developing azole resistance. However, those with a history of one or more episodes of documented oesophageal candidiasis can be considered as candidates for chronic suppressive therapy: fluconazole 100 to 200mg daily.

#### ***Special Considerations in Pregnancy***

Pregnancy increases the risk of vaginal colonisation with *Candida* species. In general, invasive or refractory oesophageal *Candida* infections should be treated the same in pregnancy as in the non-pregnant adult, with the exception that amphotericin B should be substituted for fluconazole or itraconazole (if indicated) in the first trimester if similar efficacy is to be expected.

This is because fluconazole is teratogenic in high doses in animal studies. In humans, four cases of an unusual cluster of defects (craniofacial and skeletal) have been reported after prolonged use at high doses in the first trimester of pregnancy; however, anomalies do not appear to be increased among infants born to women receiving single-dose fluconazole treatment in the first trimester. Itraconazole is teratogenic in rats and mice (skeletal defects, encephalocele, macroglossia) at high doses. Similar to fluconazole, no increase in anomalies has been noted among women exposed to treatment doses in the first trimester.

## ***CRYPTOCOCCOSIS***

### ***Epidemiology***

Virtually all HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans* var. *neoformans*. Most cases of infection are seen in patients who have CD4+ T cell counts of <50 cells/mm<sup>3</sup>. Cases of cryptococcosis have been clearly documented among HIV-infected patients in the Caribbean.<sup>xxi</sup>

### ***Clinical Manifestations***

Cryptococcosis in patients with AIDS most commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise, and headache. Classic meningeal symptoms and signs (such as neck stiffness or photophobia) occur in only about one-quarter to one-third of

patients. Some patients may present with encephalopathic symptoms such as lethargy, altered mentation, personality changes, and memory loss. Analysis of the CSF usually shows a very mildly-elevated serum protein, normal or slightly low glucose, a few lymphocytes, and numerous organisms. The opening pressure in the CSF is elevated (with pressures exceeding 200mm H<sub>2</sub>O) in up to 75% of patients. Disseminated disease is a common manifestation, with or without concurrent meningitis. About one-half of patients with disseminated disease have pulmonary rather than meningeal involvement. Symptoms and signs of pulmonary infection include cough or dyspnoea and abnormal chest radiographs. Skin lesions may be observed.

### ***Diagnosis***

Cryptococcal antigen is almost invariably detectable in the CSF at high titers in patients with meningitis or meningoencephalitis. The serum cryptococcal antigen is also usually positive and detection of cryptococcal antigen in serum may be useful in initial diagnosis. As many as 75% of patients with HIV-associated cryptococcal meningitis have positive blood cultures; if disseminated or other organ disease is suspected in the absence of meningitis, a fungal blood culture is also diagnostically helpful.

### ***Treatment Recommendations***

Untreated, cryptococcal meningitis is fatal. The recommended initial treatment for acute disease is amphotericin B, usually combined with flucytosine, for two weeks followed by fluconazole alone for a further eight weeks. This approach is associated with a mortality of less than 10% and a mycologic response of approximately 70%.

The addition of flucytosine to amphotericin B during acute treatment does not improve immediate outcome, but is well tolerated for two weeks and decreases the risk of relapse. Lipid formulations of amphotericin B appear effective. AmBisome<sup>®</sup> has been effective at doses of 4mg/kg daily. Combination therapy with fluconazole (400 to 800mg daily) and flucytosine has been effective in the treatment of AIDS-associated cryptococcal meningitis but, owing to the toxicity of this regimen (especially myelotoxicity and gastrointestinal toxicity), it is recommended only as an alternative option for those unable to tolerate or unresponsive to standard treatment.

The opening pressure should always be measured when a lumbar puncture is performed. Increased intracranial pressure may cause clinical deterioration despite a microbiologic response, probably due to cerebral oedema, and is more likely if the CSF opening pressure is >200mm H<sub>2</sub>O. In a recent large clinical trial, 93% of deaths occurring within the first two weeks of therapy and 40% of deaths occurring within weeks three through ten were associated with increased intracranial pressure. The principal intervention for reducing symptomatic elevated intracranial pressure initially is repeated daily lumbar punctures. CSF shunting should be considered for patients in whom daily lumbar punctures are no longer being tolerated or whose signs and symptoms of cerebral oedema are not being relieved. It has not yet been established that reduction in opening pressure leads to a reduction in the mortality and morbidity associated with cerebral oedema.

After a two-week period of successful induction therapy, consolidation therapy should be initiated with fluconazole administered for eight weeks or until CSF cultures are sterile. Itraconazole is an acceptable, albeit less effective, alternative.

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

A repeat lumbar puncture to assure clearance of the organism is not required for those with cryptococcal meningitis who have improvement in clinical signs and symptoms after initiation of treatment. If new symptoms or clinical findings occur after two weeks of treatment, a repeat lumbar puncture should be performed. Serum cryptococcal antigen is not helpful in management as changes in titer do not correlate with clinical response. Serial measurement of CSF cryptococcal antigen may be more useful but requires repeated lumbar punctures and is not routinely recommended for monitoring response. Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte

disturbances. Supplemental colloidal fluids may reduce the risk of nephrotoxicity during treatment. Infusion-related adverse reactions such as fever, chills, renal tubular acidosis, hypokalaemia, orthostatic hypertension, tachycardia, nausea, headache, vomiting, anaemia, anorexia, and phlebitis may be ameliorated pre-treatment with acetaminophen, diphenhydramine, and/or corticosteroids given approximately thirty minutes before the infusion. Lipid formulations of amphotericin B are less toxic. As previously indicated, those treated with fluconazole should be monitored for hepatotoxicity, though this toxicity is rare.

### ***Management of Treatment Failure***

Treatment failure is defined as clinical deterioration despite appropriate therapy (assuming increased intracranial pressure is being adequately treated as described above), the lack of improvement in signs and symptoms after two weeks of appropriate therapy, or relapse after an initial clinical response. A repeat lumbar puncture should be performed (if a shunt is not already in place) to ascertain whether or not intracranial pressure has increased. Fluconazole resistance of *C. neoformans* is exceedingly rare, and susceptibility testing is not routinely recommended.

The optimal therapy for those with treatment failure is not known. Those who have failed on fluconazole should be treated with amphotericin B with or without flucytosine as indicated above, and therapy should be continued until there is a clinical response. Higher doses of fluconazole in combination with flucytosine may also be useful. Voriconazole has activity against *Cryptococcus in vitro*; caspofungin does not.

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

Patients who have completed initial therapy for cryptococcosis should be administered lifelong suppressive treatment, unless immune reconstitution occurs as a consequence of HAART. Fluconazole is superior to itraconazole for preventing relapse of cryptococcal disease and is the preferred drug. Adult and adolescent patients appear to be at low risk for recurrence of cryptococcosis when they have successfully completed a course of initial therapy, remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained increase (e.g. six months or greater) in their CD4+ T cell counts to >100 to 200 cells/mm<sup>3</sup> after HAART. Discontinuing chronic maintenance therapy among such patients is a reasonable consideration. Maintenance therapy should be re-initiated if the CD4+ T cell count decreases to <100 to 200 cells/mm<sup>3</sup>.

### ***Special Considerations in Pregnancy***

Considerations regarding the use of amphotericin B, fluconazole, and itraconazole are the same as those for mucocutaneous and invasive candidiasis; i.e., amphotericin B should be used in the first trimester to avoid the potential for teratogenicity with fluconazole or itraconazole. Flucytosine was teratogenic in rats at high doses, but not at doses similar to human exposure. There are no reports of its use in the first trimester of pregnancy in humans. Flucytosine may be metabolised to 5-fluorouracil. It should be used in pregnancy only if clearly indicated.

## ***HISTOPLASMOSIS***

### ***Epidemiology***

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. The disease occurs in 2% to 5% of patients with AIDS from endemic areas, and has been clearly documented in the Caribbean.<sup>xxii</sup> In non-endemic areas, it most often occurs in those who have previously lived in an endemic region. Histoplasmosis is acquired by inhalation of microconidia of the mycelial phase of the organism, but re-activation of latent infection may be a mechanism for disease in some patients. Disseminated histoplasmosis usually occurs in individuals with CD4+ T cell counts of >150 cells/mm<sup>3</sup>; localised pulmonary histoplasmosis may be seen in individuals with CD4+ T cell counts of >300 cells/mm<sup>3</sup>.

### ***Clinical Manifestations***

The most common clinical presentation in patients with AIDS is disseminated multi-organ disease. Patients usually present with fever, fatigue, and weight loss; respiratory tract symptoms of cough, chest pain, and dyspnoea may occur in up to 50% of patients. Symptoms and signs may be limited to the respiratory tract for those with higher CD4+ T cell counts and localised pulmonary histoplasmosis. Fewer than 10% of patients present with a “septic shock” syndrome. CNS, gastrointestinal, and coetaneous manifestations each occur in <10% of cases, and other sites may be less commonly involved.

### ***Diagnosis***

Detection of *Histoplasma* antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated histoplasmosis but insensitive for pulmonary infection. Antigen is detected in the urine of 95% and serum of 85% of cases of disseminated histoplasmosis, and may be present in bronchoalveolar lavage fluid or CSF of patients with pulmonary or meningeal involvement. Fungal stain of blood smears or tissues may also yield a rapid diagnosis, but the sensitivity is <50%. *H. capsulatum* can be isolated from blood, bone marrow, respiratory secretions, or localised lesions in over 85% of cases, but isolation may take two to four weeks. Serologic tests are positive in over two-thirds of cases but are rarely helpful in the acute diagnosis of histoplasmosis disease. Diagnosis of meningitis poses added difficulties. Fungal stains are usually negative, and CSF cultures are positive in no more than half of cases. Antigen or anti-*Histoplasma* antibodies may be detected in the CSF in up to 70% of cases. A presumptive diagnosis of *Histoplasma* meningitis may be appropriate if the patient has disseminated histoplasmosis and findings of CNS infection cannot be explained by another cause.

### ***Treatment Recommendations***

Patients with severe disseminated histoplasmosis who meet one or more of the following criteria (temperature >39°C, systolic blood pressure <90mmHg, pO<sub>2</sub> <70 torr, weight loss >5%, Karnofsky performance score <70, haemoglobin <10gm/dl, neutrophil count <1,000/mm<sup>3</sup>, platelet count <100,000/mm<sup>3</sup>, aspartate aminotransferase >2.5 times normal, bilirubin or creatinine >2 times normal, albumin <3.5 gm/dL, coagulopathy, presence of other organ system dysfunction, or confirmed meningitis) should be treated with IV amphotericin B, either the deoxycholate formulation or liposomal amphotericin B, for the first three to ten days until they clinically improve. Liposomal amphotericin B has been more effective than the standard deoxycholate formulation, inducing a more rapid and more complete response, lowering mortality, and reducing toxicity. IV itraconazole 200mg daily after an initial loading period may be used for persons who cannot tolerate amphotericin B.

Patients responding well after completion of initial amphotericin B therapy for three to ten days may be switched to oral therapy with itraconazole capsules to complete twelve weeks of treatment and then placed on maintenance treatment as indicated below. Itraconazole solution would be logical to use, but there are no trials documenting efficacy and tolerability in this setting. Fluconazole 800mg daily is less effective than itraconazole, but is recommended as an alternative if patients cannot tolerate itraconazole.

For those with confirmed meningitis, amphotericin B should be continued for twelve to sixteen weeks followed by maintenance therapy as described below. Fluconazole has been recommended previously for HIV-uninfected individuals with meningitis following amphotericin B; however, itraconazole may be considered in this setting.

In persons with mild illness, therapy with itraconazole capsules for twelve weeks is recommended. Acute pulmonary histoplasmosis in an HIV-infected patient with intact immunity, as indicated by a CD4+ T cell count of >500 cells/mm<sup>3</sup>, may require no therapy and should be managed in a similar way to infection in an otherwise non-compromised host.

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

Patients who complete initial therapy for histoplasmosis should be administered lifelong suppressive treatment with itraconazole 200mg twice daily.

Although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their CD4+ T cell counts increase to >100 cells/mm<sup>3</sup> in response to HAART, the number of patients who have been evaluated is insufficient to warrant a recommendation to discontinue prophylaxis.

### ***Special Considerations in Pregnancy***

Treatment is the same as for non-pregnant adults. Because fluconazole has been shown to be teratogenic in high doses in animal studies, and itraconazole is teratogenic in high doses in rats and mice, amphotericin B should be substituted for itraconazole or fluconazole (if indicated) in the first trimester.

## **COCCIDIOIDOMYCOSIS**

### ***Epidemiology***

Coccidioidomycosis is caused by *Coccidioides immitis* and is seen predominantly in endemic regions, which include Central and South America; cases have been documented in the Caribbean as well.<sup>xxiii</sup> Sporadic cases may be diagnosed from non-endemic areas due to re-activation of prior infection. Both localised pneumonia and disseminated infection are usually observed in those with CD4+ T cell counts of <250 cells/mm<sup>3</sup>.

### ***Clinical Manifestations***

The two most common clinical presentations of coccidioidomycosis are disseminated disease and meningitis. Disseminated disease is associated with generalised lymphadenopathy, skin nodules or ulcers, peritonitis, liver abnormalities, and bone and joint involvement. Localised meningeal disease results in symptoms of lethargy, fever, headache, nausea or vomiting, and/or confusion, and occurs in about 10% of patients. In those with meningeal involvement, CSF analysis typically demonstrates a lymphocytic pleocytosis with CSF glucose levels of <50mg/dL. CSF protein may be normal or mildly elevated.

### ***Diagnosis***

The diagnosis of coccidioidomycosis is confirmed by culture of the organism from clinical specimens or by demonstration of the typical spherule on histopathological examination of involved tissue. Blood cultures are positive in a minority of patients. *C. immitis* serology is frequently positive in HIV-infected patients with coccidioidomycosis and is useful in diagnosis. Complement fixation serology (IgG) is generally positive in the CSF in coccidioidal meningitis.

### ***Treatment Recommendations***

For non-meningeal pulmonary or disseminated disease, amphotericin B is the preferred initial therapy. Data evaluating lipid formulations of amphotericin B are limited such that appropriate dosing recommendations cannot be made. Therapy with amphotericin B should continue until there is clinical improvement; this usually occurs after administration of 500 to 1,000mg. Some experts would use an azole antifungal concurrently with amphotericin B. Fluconazole or itraconazole may be appropriate alternatives for patients with mild disease.

Coccidioidal meningitis should be treated with fluconazole, which has been reported to be successful in approximately 80% patients with this disease. Consultation with a specialist is recommended. Intrathecal amphotericin B is the most accepted alternative but is quite toxic.

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

Patients who complete initial therapy for coccidioidomycosis should be administered lifelong suppressive therapy using either fluconazole 400mg daily or itraconazole 200mg twice daily.

Although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their CD4+ T cell counts increase to >100 cells/mm<sup>3</sup> in response to HAART, the number of patients who have been evaluated are insufficient to warrant a recommendation to discontinue prophylaxis.

### ***Special Considerations in Pregnancy***

*Coccidioides* infections appear to be more likely to disseminate if acquired during pregnancy in HIV-uninfected women, with the risk increasing with increasing gestational age.

In general, invasive fungal infections should be treated the same in pregnancy as in the non-pregnant adult, with the exception that amphotericin B is the preferred agent in the first trimester because of the potential teratogenic risks of the azoles.

## **ASPERGILLOSIS**

### ***Epidemiology***

Aspergillosis is most frequently caused by *Aspergillus fumigatus* but occasionally by other *Aspergillus* species. Specific risk factors previously identified include neutropaenia, low CD4+ T cell counts, corticosteroid use, exposure to broad-spectrum antibacterial therapy, and prior pneumonia or other underlying lung disease. Patients diagnosed with HIV-associated aspergillosis have extremely low CD4+ T cell counts (<50 cells/mm<sup>3</sup>), a history of other AIDS-defining OIs, and are not receiving HAART.

### ***Clinical Manifestations***

Two major syndromes have been described in patients with AIDS-respiratory tract disease: 1) either semi-invasive pseudomembranous tracheitis or invasive pneumonitis and 2) CNS infection presenting as a febrile diffuse meningoencephalitis syndrome with vascular infarction as a central feature (based on the predilection of *Aspergillus* organisms to invade blood vessel walls).

Semi-invasive pseudomembranous tracheitis is associated with fever, cough, dyspnoea, stridor, and wheezing due to airway constriction, culminating in airway obstruction if untreated. Endoscopic examination demonstrates a confluent, exudative pseudomembrane adherent to the tracheal wall. Invasive pneumonitis presents with fever, cough, dyspnoea, chest pain, haemoptysis, and hypoxaemia; chest radiograph demonstrates either a diffuse interstitial pneumonitis or a localised “wedge-shaped”, dense infiltrate representing pulmonary infarction, again related to the predilection of the organisms for invasion of vascular endothelium.

### ***Diagnosis***

A definitive diagnosis requires the presence of relevant clinical signs and symptoms coupled with the histopathologic demonstration of organisms in biopsy specimens obtained from involved sites or from a site that is expected to be sterile, e.g. liver or brain. A presumptive diagnosis of respiratory tract disease can be made in the absence of a tissue biopsy if *Aspergillus* sp. are cultured from a respiratory sample, a compatible lesion or syndrome is present, and no alternative causative process is identified. Serologic testing is not helpful.

### ***Treatment Recommendations***

The recommended treatment for invasive aspergillosis is voriconazole, though this agent has not been studied in HIV-infected patients with this disease. Amphotericin B, either conventional or lipid formulation, in doses equivalent to 1mg/kg daily of standard amphotericin B, is an alternative regimen. Itraconazole represents another alternative option, while caspofungin is approved for patients failing to tolerate or improve with standard therapy.

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

Rarely, airway obstruction results from extensive pseudomembrane formation in those with tracheitis. Pulmonary infarction and progressive interstitial pneumonitis may lead to respiratory failure.

### ***Management of Treatment Failure***

The overall prognosis is poor in patients with advanced immunosuppression and in the absence of effective HAART. Treatment failure is generally defined as failure to respond to initial therapy or progression of clinical signs and symptoms despite appropriate therapy. There are no data to guide recommendations for the management of treatment failure. If amphotericin B was used initially, substitution with voriconazole may be considered; similarly, substitution of amphotericin B for voriconazole would be rational for those who began therapy with voriconazole.

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

There are no data upon which to base a recommendation for or against chronic maintenance or suppressive therapy in those who have successfully completed an initial course of treatment.

#### ***Special Considerations in Pregnancy***

As with other invasive fungal infections, in general, aspergillosis should be treated the same in pregnancy as in the non-pregnant adult, with the exception that amphotericin B is the preferred agent in the first trimester due to the potential teratogenic risks of the azoles.

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

#### ***Epidemiology***

CMV is a double-stranded DNA virus in the herpes virus family that may reactivate to cause disseminated or localised end-organ disease in patients with advanced immunosuppression who have been previously infected with CMV. The majority of infections are thought to derive from re-activation of latent infection. In the era before HAART, it was estimated that 30% of patients with AIDS developed CMV retinitis some time between the diagnosis of AIDS and death. End-organ disease due to CMV occurs in persons with advanced immunosuppression, typically those with CD4+ T cell counts of  $<50$  cells/mm<sup>3</sup>, who are either not receiving or have failed to respond to HAART. Other risk factors include prior OIs, particularly MAC disease.

#### ***Clinical Manifestations***

Retinitis is the most common clinical manifestation of CMV end-organ disease in the patient population. CMV retinitis usually presents as unilateral disease, but in the absence of therapy, viraemic dissemination results in bilateral disease in the majority of patients. Peripheral retinitis may be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Central retinal lesions or lesions impinging on the macula are associated with decreased visual acuity or central field defects. The characteristic ophthalmologic appearance of CMV lesions includes perivascular fluffy yellow-white retinal infiltrates, typically described as a focal necrotising retinitis, with or without intraretinal haemorrhage, and with little inflammation of the vitreous unless immune recovery with HAART intervenes. In the absence of HAART or specific anti-CMV therapy, retinitis invariably progresses, usually within ten to twenty-one days following presentation. Progression of retinitis occurs in “fits and starts” and causes a characteristic “brushfire” pattern, with a granular, white leading edge advancing before an atrophic, gliotic scar.

Colitis is the second most common manifestation, occurring in 5% to 10% of persons with AIDS and CMV end-organ disease. The most frequent clinical manifestations are fever, weight loss, anorexia, abdominal pain, debilitating diarrhoea, and malaise. Extensive mucosal haemorrhage and perforation can be life-threatening complications.

Oesophagitis due to CMV occurs in less than 5% to 10% of persons with AIDS who develop CMV end-organ disease, causing fever, odynophagia, nausea, and occasionally mid-epigastric or retrosternal discomfort.

CMV neurologic disease causes dementia, ventriculoencephalitis, or ascending polyradiculomyelopathy. Patients with dementia typically present with lethargy, confusion,

and fever but the clinical presentation may mimic that of HIV dementia. The CSF generally demonstrates lymphocytic pleocytosis (although a mixture of neutrophils and lymphocytes may be seen), low to normal glucose levels, and normal to elevated protein levels. Patients with ventriculoencephalitis have a more acute course, with focal neurologic signs, often including cranial nerve palsies or nystagmus. There is a rapid progression to death. Periventricular enhancement of CT or MRI images is suggestive of CMV ventriculoencephalitis rather than HIV-related neurologic disease. CMV polyradiculomyelopathy causes a Guillan Barré-like syndrome characterised by urinary retention and progressive bilateral leg weakness. The clinical symptoms generally progress over several weeks to include loss of bowel and bladder control and flaccid paraplegia. A spastic myelopathy has been reported and sacral paresthesia may occur. The CSF generally shows a neutrophilic pleocytosis (often there are 100 to 200 neutrophils/mm<sup>3</sup> and some erythrocytes), accompanied by low CSF glucose and elevated protein levels.

CMV pneumonitis is uncommon, but when it occurs, it presents with shortness of breath, dyspnea on exertion, a non-productive cough, and hypoxaemia, associated with interstitial infiltrates on chest radiograph.

### ***Diagnosis***

The diagnosis of CMV retinitis is generally made based on recognition of characteristic retinal changes observed on funduscopic examination by an experienced ophthalmologist.

The demonstration of mucosal ulcerations on endoscopic examination, coupled with colonoscopic or rectal biopsy demonstrating histopathological identification of characteristic intranuclear and intracytoplasmic inclusions are required for the diagnosis of CMV colitis.

The diagnosis of CMV oesophagitis is established by the presence of extensive large, shallow ulcers of the distal oesophagus and by biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the ulcer's edge. Culturing CMV from a biopsy or cells brushed from the colon or the oesophagus is not sufficient to establish the diagnosis of CMV colitis or oesophagitis because some persons with low CD4<sup>+</sup> T cell counts may be viremic and have positive cultures for CMV in the absence of clinical disease.

CMV neurologic disease is diagnosed on the basis of a compatible clinical syndrome and on the presence of CMV in CSF or brain tissue. Detection of CMV in CSF is greatly enhanced by PCR testing.

Diagnosis of CMV pneumonitis should be made in the setting of pulmonary interstitial infiltrates, through identification of multiple CMV inclusion bodies in lung tissue, and by the absence of other pathogens that are more commonly associated with pneumonitis in this population.

### ***Treatment Recommendations***

The choice of initial therapy for CMV retinitis should be individualised, based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. Oral valganciclovir, IV ganciclovir, IV ganciclovir followed by oral valganciclovir, IV foscarnet, IV cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective alternatives, as summarised in *Appendix B*. Prior to the availability of HAART, these medications were administered for CMV retinitis in a course of acute induction therapy, followed by secondary prophylaxis (chronic maintenance therapy) for life--prohibitively expensive for many Caribbean settings. However, with the increasing availability of HAART, simultaneous initiation of acute induction therapy together with HAART has become an attractive option. This offers the possibility of stopping the progression of CMV retinitis to preserve vision, followed by a time-limited course of maintenance therapy, with the potential for discontinuing the maintenance therapy after a sustained (six months or greater) increase in CD4<sup>+</sup> T cell counts to >100 cells/mm<sup>3</sup> in response to HAART.

Some clinicians would not treat small peripheral CMV retinitis lesions if HAART is soon to be initiated, as immune recovery may ultimately control the retinitis. However, there is a suggestion that immune recovery uveitis (IRU) is more common among patients given less aggressive anti-CMV therapy. Similarly, some HIV specialists would withhold therapy for mild to moderately severe CMV colitis or oesophagitis if HAART is soon to be initiated or can be optimised unless moderate to severe symptoms justify the use of systemic anti-CMV therapy treatment.

There are no data demonstrating that starting HAART in treatment-naïve patients with CMV retinitis would have an adverse effect on retinitis, gastrointestinal disease, or pneumonitis, or worsen IRU should this occur. Thus, there is no reason to delay initiation of appropriate HAART, which should be administered based on standards of care in the community, to those with acute CMV retinitis, gastrointestinal disease, or pneumonitis.

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

Management of CMV retinitis requires close monitoring by an experienced ophthalmologist as well as by the primary clinician. Dilated indirect ophthalmoscopy should be performed at the time of diagnosis of CMV retinitis, after completion of induction therapy, one month after the initiation of therapy, and monthly thereafter while the patient is on anti-CMV treatment. Adverse effects of anti-CMV medications are summarised in *Appendix D*.

IRU is an immunologic reaction to CMV characterised by inflammation in the anterior chamber and/or vitreous in the setting of immune reconstitution, and is generally observed in those with a substantial rise in CD4+ T cell counts in the four to twelve weeks following initiation of HAART. Ocular complications of uveitis include macular oedema and epiretinal membranes, which can cause loss of vision. Treatment usually requires periocular corticosteroids or short courses of systemic corticosteroids. Estimated response rates are about 50%.

### ***Special Considerations in Pregnancy***

Indications for treatment of CMV infection during pregnancy are the same as for those in non-pregnant HIV-infected adults. For retinal disease, use of intraocular implants or intravitreal injections for local therapy should be considered in pregnancy if possible to limit foetal exposure to systemically administered antiviral drugs.

Ganciclovir is embryotoxic in rabbits and mice and teratogenic (cleft palate, anophthalmia, aplastic kidney and pancreas, hydrocephalus) in rabbits. There are case reports of safe use in human pregnancy after organ transplantation.

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

### ***Epidemiology***

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common. Herpes simplex virus infections in the Caribbean have been well-described in several studies of HIV-negative persons and also in one Jamaican study of immunocompromised HIV-infected patients.<sup>xxiv</sup> As many as 95% of HIV-infected persons are seropositive for either HSV-1 or HSV-2, although in most infected persons, HSV infections are asymptomatic. Regardless of the clinical severity of infection, reactivation on mucosal surfaces occurs intermittently and can result in transmission.

### ***Clinical Manifestations***

HSV orolabialis is the most common manifestation of HSV-1 infection, presenting with a sensory prodrome in the affected area, rapidly followed by the evolution of lesions from papule to vesicle, ulcer, and crust stages on the lips. Ulcerative lesions are usually the only stage observed on mucosal surfaces. The course of illness in untreated subjects is seven to ten days; lesions recur one to twelve times per year and can be triggered by sunlight or physiologic stress.

HSV genitalis is the more common manifestation of HSV-2 infection. Genital mucosal or skin lesions are similar in appearance and evolution to external orofacial lesions. Local symptoms include a sensory prodrome consisting of pain and pruritis. Ulcerative lesions are usually the only stage observed on mucosal surfaces. Mucosal disease is occasionally accompanied by dysuria and vaginal or urethral discharge; inguinal lymphadenopathy, particularly in primary infection, is common with genital herpes. In profoundly immunocompromised patients, extensive, deep, non-healing ulcerations may occur. These lesions have been most often reported in those with CD4<sup>+</sup> T cell counts of <100 cells/mm<sup>3</sup> and also might be more commonly associated with acyclovir resistant virus. HSV encephalitis occurs among HIV-infected persons, but no evidence exists to suggest that it is more severe or common than among HIV-uninfected persons.

### ***Diagnosis***

Though HSV infections are often diagnosed and treated empirically on the basis of characteristic skin, mucus membrane, or ophthalmic lesions, laboratory confirmation is required to definitively diagnose mucosal HSV infection. Viral culture, HSV DNA PCR, or HSV antigen detection are available methods for diagnosis of mucocutaneous lesions caused by HSV. Type-specific serologic assays that distinguish between HSV-1 and HSV-2 antibody can be used in asymptomatic persons or those with atypical lesions.

### ***Treatment Recommendations***

Orolabial lesions can be treated with oral famciclovir, valacyclovir, or acyclovir for five to ten days (AII). Severe mucocutaneous HSV lesions are best treated initially with IV acyclovir (435--437) (AII). Patients may be switched to oral therapy after the lesions have begun to regress; therapy should be continued until the lesions have completely healed. Initial or recurrent genital HSV should be treated with oral famciclovir, valacyclovir, or acyclovir for seven to fourteen days (AII).

Trifluridine and IV acyclovir are indicated for the treatment of herpes keratitis and HSV encephalitis, respectively. These conditions should be treated in consultation with an expert in HSV management.

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

Famciclovir, valacyclovir, and acyclovir are generally well-tolerated but are occasionally associated with nausea or headache. Rarely, patients receiving higher doses of famciclovir, valacyclovir, or acyclovir might experience renal dysfunction. For patients receiving high-dose IV acyclovir, monitoring of renal function is recommended at initiation of treatment, and once or twice weekly for the duration of treatment particularly for those with underlying renal dysfunction or those receiving prolonged therapy. Thrombotic thrombocytopenic purpura-haemolytic uremic syndrome resulting in death has been reported among HIV-infected patients treated with high-dose (8g/day) valacyclovir but has not been reported at doses used for therapy of HSV infection.

### ***Management of Treatment Failure***

Treatment failure related to resistance to antiviral drugs should be suspected if lesions do not indicate signs of resolution within seven to ten days after initiation of therapy. Among immunocompromised patients with suspected acyclovir resistant HSV, a lesion culture should be obtained and, if the virus is isolated, susceptibility testing performed to confirm drug resistance. Foscarnet is the treatment of choice for acyclovir resistant HSV. Topical trifluridine or cidofovir also has been used successfully for lesions on external surfaces, although prolonged application for twenty-one to twenty-eight days or longer may be required.

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

Chronic therapy with acyclovir is not required after lesions resolve. However, most recurrences can be prevented by use of daily anti-HSV therapy and is recommended for persons who have frequent or severe recurrences.

### ***Special Considerations in Pregnancy***

Acyclovir is the first choice for therapy of HSV infections in pregnancy. The predominant risk, regardless of HIV-co-infection, is from maternal genital shedding at delivery. Caesarean delivery is recommended for women with prodrome or visible HSV genital lesions at the onset of labour.

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

### ***Epidemiology***

Up to 95% of the adult population is seropositive for VZV, and recurrent disease in the form of herpes zoster occurs in 3% to 5% of all adults but becomes more prevalent in the elderly and the immunocompromised host. The incidence of herpes zoster is fifteen to twenty-five times greater in HIV-infected persons than in the general population, and three to seven times greater in the elderly. Zoster in HIV-infected adults can occur at any CD4+ T cell count; more advanced immunosuppression may be associated with altered manifestations of VZV infection as described below, but does not appear to substantially alter the overall incidence of VZV.

### ***Clinical Manifestations***

Herpes zoster (*shingles*) may follow a prodrome of pain that resembles a burn or muscle injury in the affected dermatome; skin lesions, which are similar to chickenpox in appearance and evolution, develop in the same dermatome. Extensive coetaneous dissemination and visceral involvement occur rarely.

Progressive outer retinal necrosis is a VZV-associated entity that typically occurs in HIV-infected persons with CD4+ T cell counts of  $<50$  cells/mm<sup>3</sup>. This rapidly-progressive necrotising herpetic retinopathy is often associated with dermatomal zoster and is characterised by multifocal retinal opacification with little or no ocular inflammation and rapid visual loss.

VZV has been associated with transverse myelitis, encephalitis, and vasculitic stroke in HIV-uninfected individuals. There are rare anecdotal reports of these syndromes in HIV-infected patients.

### ***Diagnosis***

Zoster and chickenpox are generally diagnosed empirically based on the appearance of characteristic lesions.

### ***Treatment Recommendations***

The recommended treatment for localised dermatomal herpes zoster is acyclovir, famciclovir, or valacyclovir for seven to ten days. If coetaneous lesions are extensive or if there is clinical evidence of visceral involvement, IV acyclovir should be initiated and continued until coetaneous lesions and visceral disease are clearly resolving. Due to its immunosuppressive effects and the absence of data to support benefit with its use in this patient population; adjunctive corticosteroid therapy to prevent post-herpetic neuralgia is not recommended.

Progressive outer retinal necrosis is rapidly progressive and leads to profound loss of vision. Because of the rapidity of disease progression, recommended treatment is with high-dose IV acyclovir in combination with foscarnet.

IV acyclovir for seven to ten days is the recommended initial treatment for immunocompromised adults and adolescents with chickenpox. It may be permissible to switch to oral therapy after the patient has defervesced if there is no evidence of visceral involvement. Oral acyclovir is the recommended oral treatment (20mg/kg up to a maximum dose of 800mg four times daily), but valacyclovir or famciclovir would be reasonable alternatives.

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

Same as for HSV.

### ***Management of Treatment Failure***

Treatment failure due to drug resistance should be suspected if lesions do not show signs of resolution within ten days of initiation of therapy or if they evolve to a verrucous appearance. In patients with suspected or proven acyclovir resistant VZV infections, treatment with IV foscarnet is the recommended alternative therapy.

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

No drug has been proven to prevent the recurrence of zoster among HIV-infected individuals.

### ***Special Considerations in Pregnancy***

Treatment of zoster in pregnancy should be the same as for non-pregnant adults.

## ***HUMAN HERPESVIRUS-8 (HHV-8) DISEASE***

### ***Epidemiology***

Human herpesvirus-8 (HHV-8) is a transmissible DNA virus with a seroprevalence in the United States of 1% to 5%. The seroprevalence is considerably greater among MSM regardless of HIV infection, and is also much higher in certain Mediterranean countries (10% to 20%) and in parts of sub-Saharan Africa (30% to 80%). The dermatovenereology clinic at the Princess Margaret Hospital in Nassau has documented three cases of KS all involving the lower limbs in HIV-infected young men (Orlander and Woods-Cargill, personal communication). HHV-8 is associated with all forms of KS (classic, endemic, transplant-related, and AIDS-related), as well as certain rare neoplastic disorders such as primary effusion lymphoma and multicentric Castleman's disease. The precise pathogenesis is unclear even though seroconversion to HHV-8 precedes the development of these tumours.

There are anecdotal reports of lesion regression in patients who have been treated with HAART, and the overall incidence of KS has declined dramatically in the United States following the introduction of PIs and HAART.

KS, primary effusion lymphoma, and multicentric Castleman's disease are described most frequently in HIV-infected persons with more advanced immunosuppression (CD4+ T cell counts of <200 cells/mm<sup>3</sup>), although they can occur at any CD4+ T cell count level.

### ***Clinical Manifestations and Treatment***

As the principal clinical manifestations of HHV-8 infection are neoplastic diseases, the presentation, diagnosis, and treatment recommendations for these entities are beyond the scope of this document. HAART that suppresses HIV replication reduces the frequency of occurrence of KS among HIV-infected persons and should be considered for all persons who qualify for such therapy.

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

Effective suppression of HIV replication with HAART among HIV-infected patients with KS might prevent KS progression or occurrence of new lesions and should be considered for all persons with KS.

### ***Special Considerations in Pregnancy***

The seroprevalence of HHV-8 infection among HIV-infected pregnant women does not appear to impact pregnancy outcome.

## ***PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) DUE TO JC VIRUS***

### ***Epidemiology***

PML is an AIDS-defining neurologic disease caused by the JC virus, a ubiquitous polyoma virus; the name is derived from the initials of the first patient from which this virus was isolated. Most humans are infected early in life, and most adults have detectable serum antibodies.

### ***Clinical Manifestations***

PML is the only known disease caused by the JC virus. This disease has an insidious onset and produces a neurologic syndrome that progresses relatively rapidly over weeks or months characterised by cognitive dysfunction, dementia, seizures, ataxia, aphasia, cranial nerve deficits, hemiparesis or quadriparesis, and eventually coma. Typical CT abnormalities include single or multiple hypodense, non-enhancing cerebral white matter lesions, although cerebellum and brain stem are occasionally involved.

### ***Diagnosis***

A confirmed diagnosis of PML requires a compatible clinical syndrome and radiographic findings coupled with a brain biopsy demonstrating characteristic pathologic foci of demyelination and oligodendrocytes with enlarged nuclei and basophilic-staining intranuclear material. Whether a brain biopsy will yield information that will alter the clinical course of a patient presenting with a demyelinating disease is a clinical judgment.

### ***Treatment Recommendations***

There is no effective therapy for JC virus. However, when HAART is initiated and CD4+ T cell counts rise, some patients will experience neurologic improvement. Others may simply become neurologically stable. There are several reports, however, of patients developing worse neurologic manifestations after initiation of HAART. In some instances, this worsening is due to inflammatory IRS; other cases represent simply the natural history of PML.

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

### ***Epidemiology***

HPV infection of the genital tract and anus results in a spectrum of disease ranging from self-limited, transient infection to squamous cell cancer.

HPV is the aetiologic agent of genital warts (condyloma acuminata). Only a small number of HPV types produce warts on the external genital or anal skin; types 6 and 11 account for nearly 90% of such lesions. The incidence of genital warts is increased by more than ten times in HIV-infected women compared with uninfected women.

In parallel with the increased prevalence of genital HPV infection, cervical intraepithelial neoplasia (CIN), and anal intraepithelial neoplasia (AIN) associated with certain other HPV subtypes (16, 18, 31, 35 and others), occur with increased frequency in HIV-infected women compared with HIV-uninfected women. A 2000 study of female sex workers (FSW) in Guyana found that HIV-positive women have anal sex more frequently and would therefore also be at risk for anal HPV infection.<sup>xxv</sup> The relative risk of CIN is increased five- to ten-fold for HIV-positive women, and the risk of cervical cancer may also be increased.

HIV-infected women with CIN manifest higher grade lesions than HIV-negative women, particularly those with lower CD4+ T cell counts and higher plasma HIV RNA levels, and are at higher risk of having HPV-associated lesions elsewhere in the vagina, vulva, and anus.

MSM have a high prevalence of anal HPV infection and of AIN, and those who are HIV-infected, particularly those with lower CD4+ T cell counts, are at an even higher risk. The incidence of anal cancer is also higher in MSM than in the general population.

### ***Clinical Manifestations***

The principal manifestations of genital and anal HPV infections are the presence of genital or anal warts or of CIN or AIN detected by cytology or inspection with magnification (e.g. colposcopy or anoscopy). In HIV infection with immunosuppression, genital and anal warts sometimes grow much larger and increase greatly in number and may extend to involve a large area of epithelium.

### **Diagnosis**

HPV disease can be diagnosed by clinical inspection. The entire anal and genital areas should be carefully inspected for visual signs of warts. Digital examination should be performed after collection of a cervical Papanicolaou smear, as lubricant may obscure the interpretation of Pap smears.

Testing for HPV DNA is available, but there is currently no clinical indication for routine testing of anogenital warts for the presence or type of HPV. Current guidelines should be followed for routine Pap smear monitoring to detect cervical dysplasia in HIV-infected women. If a Pap smear is performed and returns with a cytologic interpretation reporting *atypical squamous cells of uncertain significance* (ASCUS) or *atypical squamous cells-cannot rule out high-grade disease* (ASC-H), or a low-grade squamous intraepithelial lesion (LSIL) or a high grade SIL (HSIL), colposcopic evaluation and directed biopsy are recommended.

Although formal guidelines recommending anal Pap smear screenings have not been adopted, anal cytologic screenings should be considered for HIV-infected men and women. High-resolution anoscopy (HRA) should be considered if the anal Pap smear shows ASCUS or ASC-H and should be performed if an individual has LSIL or HSIL on an anal Pap smear. Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer.

### **Treatment Recommendations**

There are a number of treatments available for genital warts, but none are uniformly effective. Recurrences are frequent with most modalities. There are limited data on the response of HIV-infected patients to the available treatments for genital warts. The treatment options are briefly summarised below, divided into patient-applied treatments and provider-applied treatments.

Patient-applied treatments are generally recommended for uncomplicated external lesions and consist of the following options:

- ❖ Podofilox is an anti-mitotic agent that should be applied topically to wart lesions as a 0.5% solution or a 0.5% gel; twice-daily applications for three consecutive days can be repeated weekly for up to four weeks. The efficacy is 40% to 60% in immunocompetent subjects.
- ❖ Imiquimod recruits an inflammatory response to the site of the wart. A 5% cream formulation is applied to lesions at bedtime and removed in the morning by washing. The drug should be applied on three non-consecutive nights weekly for up to sixteen weeks. The efficacy of imiquimod in immunocompetent individuals is 30% to 70%; the overall response in HIV-positive individuals may be lower than in immunocompetent persons.

Provider-applied treatments are generally recommended for complex or multentric lesions or those lesions inaccessible to patient-applied treatments. Options are summarised as follows:

- ❖ Cryotherapy with liquid nitrogen should be applied until each lesion is thoroughly frozen. Some experts recommend allowing the lesion to thaw and freezing a second time in each session. Cryotherapy sessions can be repeated every one to two weeks up to three to four times. The efficacy of cryotherapy is 60% to 80%.
- ❖ Trichloroacetic or bichloroacetic acids act as caustic agents to kill wart tissue. They can be made in an 80% to 95% aqueous solution and applied to each lesion. The treatment can be repeated weekly for three to six weeks. The expected efficacy is 60% to 80%.
- ❖ Surgical treatments include excision by scissor, shave, curette, or electrosurgery. The efficacy of surgical removal can approach 100% depending on the location of the lesions.

- ❖ Podophyllin resin is a crude extract that contains podophyllotoxin and other cytotoxins and induces wart necrosis after topical application. It is prepared as a 10% to 25% suspension in tincture of benzoin. It is applied by the provider to all lesions (up to 10 cm<sup>2</sup> of skin area) and then removed by washing a few hours later. Applications can be repeated weekly for three to six weeks. Efficacy ranges from 20% to 80%.

In general, the management of CIN in HIV-infected patients does not differ from management in other women. Most experts recommend observation without specific intervention for CIN 1 unless lesions persist over an eighteen to twenty-four month period of follow-up, evolve to CIN 2 or worse, or there is poor adherence to routine monitoring. Conventional therapies used for treatment of CIN 2 or 3 include cryotherapy, laser therapy, cone biopsy, and a loop electrosurgical excision procedure (LEEP)--generally the preferred mode of treatment. Recurrence rates of 40% to 60% after treatment have been reported in HIV-infected women undergoing these procedures.

For anal condyloma and AIN, there are insufficient data to recommend a specific treatment approach, although experienced clinicians follow approaches listed in *Table 4*.

**Table 4: Treatment of Anal Condyloma or Anal Intraepithelial Neoplasia (AIN)**

<b>A. CONDYLOMA OR AIN-1</b>	<b>LESION LOCATION</b>	
	<u>Perianal</u>	<u>Intra-Anal</u>
<u>Lesion Size</u>		
Discrete, <1cm <sup>2</sup> at base	A,B,C,D,E	A,B,E,F,G,H
Discrete lesion >1cm <sup>2</sup> at base, not circumferential	A,B,C,D,E,F,G,H	E,F,G,H
Diffuse or circumferential lesions	C,D,E,F,G,H	H
<b>B. AIN-2/AIN-3</b>		
<u>Lesion Size</u>	<u>Perianal</u>	<u>Intra-Anal</u>
Discrete, <1cm <sup>2</sup> at base	A,B,E,F	A,B,E,F,G
Discrete lesion >1cm <sup>2</sup> at base, not circumferential	E,F,G	E,F,G
Diffuse or circumferential lesions	E,F,G,H	H

**Key:**

- A: 85% trichloroacetic acid
- B: Liquid nitrogen
- C: Imiquimod
- D: Podophyllotoxin
- E: Electrocautery
- F: Laser
- G: Surgical cold scalpel excision
- H: Observation only

There is no evidence to suggest that HAART should be instituted or modified for the sole purpose of treating CIN or AIN, although there are limited data to suggest that HAART may be associated with improved response rates.

**Monitoring and Adverse Effects**

Recurrences of CIN and cervical cancer after conventional therapy are more frequent in HIV-infected individuals; therefore, patients should be carefully followed after treatment with frequent cytologic screening and colposcopic examination when indicated as per published guidelines.

**Prevention of Recurrence**

There is currently no indication for secondary prophylaxis with any of the conventional modalities to prevent recurrence of genital warts. Patients with CIN should be monitored with frequent cytologic screening and, when indicated, colposcopic examination for recurrent lesions.

**Special Considerations in Pregnancy**

Podophyllin and podofilox should not be used in pregnancy. Use of podophyllin has been associated with an increased risk of foetal death in several animal models and with case

reports in humans but not with congenital anomalies. No experience with imiquimod in human pregnancy has been reported, so its use in pregnancy is not recommended.

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

### ***Epidemiology***

HBV is the leading cause of chronic liver disease worldwide. In developed countries, HBV shares risk factors for transmission, such as sexual contact and injection drug use, and is transmitted more efficiently than HIV. Although up to 90% of HIV-infected persons have at least one serum marker of prior exposure to HBV, only approximately 10% have chronic HBV, as evidenced by the detection of hepatitis B surface antigen (HBsAg) in the serum persisting for a minimum of six months.

HIV infection is associated with an increased risk for the development of chronic HBV after HBV exposure. Limited data suggest that co-infected patients with chronic HBV have higher HBV DNA levels and are more likely to have detectable HBeAg, accelerated loss of protective hepatitis B surface antibody (anti-HBs), and an increased risk of liver-related mortality and morbidity.

### ***Clinical Manifestations***

While many patients are asymptomatic, symptoms of acute HBV infection include fatigue, right upper quadrant abdominal pain, nausea, vomiting, fever, and arthralgias, followed by jaundice. Although persons with chronic HBV may have non-specific symptoms such as fatigue and right upper quadrant abdominal pain, chronic HBV is often clinically inapparent until the onset of end-stage liver disease (ESLD) manifested as ascites, coagulopathy, caput medusa, palmar erythema, jaundice, hepatomegaly, splenomegaly, variceal bleeding, or hepatic encephalopathy. Ancillary manifestations of chronic HBV also include polyarteritis nodosa, glomerulonephritis, and vasculitis.

### ***Diagnosis***

All HIV-infected individuals should be tested for HBV. The optimal testing strategy for co-infected individuals has not been determined. Testing for HBsAg, hepatitis B core antibody (anti-HBc), and anti-HBs is recommended as this strategy will detect the majority of persons chronically infected with HBV, although serum HBV DNA has been detected in some persons without HBsAg; in addition, in some persons anti-HBc may be the only serum marker of infection. The interpretation of an isolated anti-HBc is difficult both because false positive tests for anti-HBc occur and because the clinical significance of anti-HBc alone or with low levels of HBV DNA, even in those with elevated ALT (alanine aminotransferase) levels, is not known.

Chronic HBV infection is defined as positive serologies for HBsAg and total anti-HBc but negative for IgM anti-HBc, or persistence of HBsAg for six or more months. Patients with chronic HBV infection should be tested for HBeAg and antibody to HBeAg (anti-HBe). Some experts would also obtain a test for circulating HBV DNA in patients diagnosed with chronic HBV. A number of assays for HBV DNA are available, but results are not interchangeable. Viral loads are usually high in chronic infection,  $10^8$ – $10^{10}$  copies/mL of blood; however, available data indicate that HBV DNA levels do not predict progression of liver disease or response to therapy in a manner analogous to plasma HIV RNA levels.

Severity of liver disease should be assessed initially and at least every six months with ALT, albumin, prothrombin time, platelet count, complete blood count, and bilirubin. Transient or persistent elevations in liver transaminases may occur just prior to loss of HBeAg; upon discontinuation of anti-HBV therapy, in association with 3TC resistance; with hepatotoxicity from anti-HIV therapy or other drugs; or with the acquisition of another hepatitis virus infection such as hepatitis A virus (HAV), hepatitis C virus (HCV), or hepatitis delta virus (HDV).

Patients with chronic HBV are at increased risk for hepatocellular carcinoma (HCC). In HIV-negative patients, some experts recommend monitoring patients with chronic HBV every six to twelve months with an alfa-fetoprotein (AFP) and/or ultrasound of the liver, especially if the patient is in a high-risk group (e.g. age forty-five years or older, cirrhosis, or a family history of HCC); however, the effectiveness of this screening strategy has not been determined. In HIV-infected patients, the risk and natural history of HBV-related HCC have not been studied, hence the optimal HCC screening method and interval are not known.

Liver biopsy remains the only definitive test to assess the grade (necro-inflammatory activity) and stage (degree of fibrosis) of liver disease. The rate of progression of chronic HBV in patients with HIV-co-infection has not been studied, and the optimal indications for liver biopsy are not known. However, because fibrosis grade and stage are currently the most reliable means to assess prognosis and to inform decisions regarding the need for initiation of therapy, in the absence of a contraindication, most experts recommend a liver biopsy for all HIV-infected persons with chronic HBV-co-infection who are candidates for antiviral therapy (see below). Some HIV specialists would initiate therapy for chronic HBV without a pretreatment liver biopsy.

### ***Treatment Recommendations***

All patients with chronic HBV should be advised to avoid or limit alcohol consumption due to the effects of alcohol on the liver. In addition, they should be counselled about the risk of household, sexual, and needle-sharing transmission and the need for such contacts to be vaccinated against HBV B infection.

Because fulminant hepatic failure from HAV infection occurs at increased frequency in persons with chronic liver disease, vaccination is indicated for persons susceptible to HAV. If possible, the vaccine should be administered before the CD4+ T cell count declines to <200 cells/mm<sup>3</sup> in order to maximise the likelihood of a response.

Antiviral treatment is recommended for patients who have any of the following: 1) actively replicating virus in blood (as defined by a positive HBeAg or HBV DNA levels of >10<sup>5</sup> copies/mL), 2) an elevated serum ALT (at least two times the upper limit of normal), or 3) histopathologic evidence of moderate disease activity and/or fibrosis on liver biopsy. The response to therapy is poor for those with a pretreatment ALT level of less than two times the upper limit of normal; hence, therapy should generally be deferred in such patients. The goals of anti-HBV therapy are sustained suppression of HBV replication, prevention of liver disease progression, and clearance of HBeAg. Treated patients rarely become HBsAg-negative as HBV reservoirs are not affected by anti-HBV therapy. There are only very limited data to suggest that treatment reduces the risk of HCC.

There is no “preferred” treatment that can be uniformly recommended for all HIV-co-infected persons with chronic HBV. Therapy should be individualised taking into account patient-specific considerations.

For HIV-infected persons who are HAART-naïve and require HAART, 3TC 150mg twice daily is the preferred treatment for chronic HBV because of its relative safety, anti-HIV activity, wealth of data regarding its use in HIV-infected individuals, and the potential toxicity associated with IFN-alfa. 3TC should be used together with other ARV drugs in a fully suppressive HAART regimen. Due to the high rate of development of HBV resistance to 3TC monotherapy, some experts further recommend the use of 3TC in combination with either adefovir or tenofovir (TDF) (as described below), although data are limited to support this approach.

Seroconversion of HBeAg occurs in 22% of HBeAg-positive, HIV-infected patients with chronic HBV who are treated with 3TC for one year. In HIV-negative patients, HBeAg seroconversions are sustained in approximately 80% if 3TC is continued several months after seroconversion. Based on limited data on the duration of treatment, HBeAg-positive, HIV/HBV-co-infected patients who become HBeAg-negative and anti-e-positive on 3TC

therapy should be treated for a minimum of one year, or at least six months beyond HBeAg seroconversion. In HIV-negative, HBeAg-negative patients with chronic HBV who are treated with 3TC, ALT and HBV DNA levels may decline, but high rates of relapse have been reported when therapy is stopped. Thus, the optimal duration of treatment of HBeAg-negative patients, whether HIV-infected or not, is unknown.

Adefovir dipivoxil, 10mg daily, has no anti-HIV activity at this dose and is unlikely to select for HIV resistance; thus, it is an appropriate alternative to interferon alfa for co-infected patients who require treatment for chronic HBV but do not yet require HAART. However, the long-term safety of adefovir has not been established in HIV-infected individuals.

TDF has similar *in vitro* anti-HBV activity to adefovir, and limited human data suggest it is also active against 3TC resistant HBV. Although TDF is not approved for use in the treatment of HBV infection and there are sparse data in HIV/HBV-co-infected patients, some experts would use TDF for both the treatment of HIV infection and chronic HBV (in conjunction with a fully suppressive HAART regimen). Until long-term data are available that demonstrate the absence of HBV resistance, it may be prudent to use TDF in combination with 3TC. TDF, if used for treatment of HBV in patients receiving HAART, should be added as a single agent for this purpose only if plasma HIV RNA levels are undetectable to avoid selection pressure that engenders drug resistance. If therapy is indicated for HIV infection but not for chronic HBV, some experts would withhold TDF, if possible, to allow for its future use for treatment of HBV.

For HBV treatment-naïve patients who require treatment of both HIV infection and chronic HBV, many experts would recommend use of a HAART regimen that includes 3TC, adefovir, or TDF, or a combination of 3TC with either adefovir or TDF, although combination therapy for treatment of HBV in this population is not yet supported by data.

Emtricitabine (FTC) (200mg once daily) is also active against HBV replication and thus could potentially be substituted for 3TC, but there are sparse data for its use for this indication and it is not active against 3TC resistant HBV.

IFN-alfa 2a and 2b, administered in subcutaneous doses of 5MU daily or 10MU three times per week, are approved for the treatment of chronic HBV in HIV-uninfected individuals but not in HIV-infected patients. IFN-alfa should not be used in patients with decompensated liver disease. Approximately one-third of HIV-negative patients will clear HBeAg with either of these interferon regimens, and the response is durable in 80% to 90% of persons followed for four to eight years. If used for treatment in HBeAg-positive patients, sixteen to twenty-four weeks of therapy is recommended, whereas for HBeAg-negative patients (who respond less well), a minimum of twelve months and possibly longer is recommended. Patients who have a substantial decrease (some experts suggest  $>2 \log_{10}$  copies/ml) or clearance of HBV DNA in response to IFN-alfa 2a or 2b at week sixteen but have persistent HBeAg may also be candidates for longer-term treatment of twelve months or longer; however, the data are insufficient to make a firm recommendation in HIV-infected patients. Studies of pegylated interferon alpha in HIV-uninfected patients with chronic HBV are in progress, and it will likely become the preferred interferon formulation.

Some experts recommend that IFN-alfa be used in HIV-co-infected patients who are candidates for treatment for chronic HBV but not HIV. This strategy preserves 3TC and/or TDF for later treatment of HIV and avoids some potential complications of HAART. The combination of 3TC and interferon does not appear to be superior to either medication alone and is not recommended.

In patients infected with HBV, HCV, and HIV, consideration of the need for HAART should be the first priority. If HAART is not required, the treatment of HCV should be considered before HBV treatment because IFN therapies for HCV may also treat HBV. If IFN-based therapy for HCV has failed, treatment of chronic HBV therapy with nucleoside or nucleotide analogs can be considered.

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

A virologic response is defined as a substantial (some experts suggest  $>2 \log_{10}$  copies/mL) decrease in HBV DNA and loss of HBeAg at the end of treatment. A sustained virologic response is defined as a decrease in HBV DNA and loss of HBeAg sustained for more than six to twelve months after the end of treatment. In HIV-uninfected persons, the response rates to IFN-alfa or 3TC-containing regimens are 50% or greater in patients with ALT levels more than five times the upper limit of normal, and 20% to 35% in patients with ALT levels between two to five times the upper limit of normal. Patients for whom therapy is not initiated should be monitored regularly for changes in ALT levels (e.g. every four to six months).

Other markers of treatment success include improvement in liver histology, normalisation of hepatic transaminases, and, in those with loss of HBeAg, the development of HBe antibody (*HBeAg seroconversion*). Sustained loss of HBsAg is considered by some to be a “complete response.” Although a decline in HBV viral load correlates with response, no threshold HBV viral load has been established that clearly defines a virological response.

Hypo- or hyperthyroidism, which may be irreversible, may occur three to six months after initiation of therapy with IFN-alfa, hence a serum TSH level should be monitored at baseline and periodically (e.g. every three months) for the duration of treatment. Side effects of IFN-alfa include flu-like symptoms (fever, headaches, chills, nausea) and fatigue, which can be reduced by premedication with acetaminophen or a non-steroidal medication. Other common side effects include weight loss, alopecia, thrombocytopenia, anaemia, leukopenia (decreased total CD4+ T cell count but not percent), depression, and auto-immune disorders.

Adefovir causes renal tubular disease and renal excretion of carnitine in a substantial proportion of patients at higher doses, but these side effects are uncommon at the 10mg per day dose. Significant renal toxicity with TDF has not been reported, although isolated cases of increased serum creatinine or renal tubular dysfunction have been observed. Given the potential for overlapping toxicities and their similar structure, TDF and adefovir should not be used in combination.

Once anti-HBV therapy with 3TC, adefovir, or TDF is begun, whether for the purpose of treating chronic HBV or for the treatment of HIV infection, discontinuation is associated with a flare of liver disease in approximately 15% of cases, with loss of the benefit accrued from prior anti-HBV treatment. Some experts recommend that once anti-HBV therapies are begun, they should be continued unless contra-indicated or unless the patient has been treated for more than six months beyond loss of HBeAg positivity. However, the risks and benefits of this practice are unknown. If anti-HBV therapy is discontinued and a flare occurs, reinstitution of anti-HBV therapy is appropriate since it can be potentially life saving.

### ***Management of Treatment Failure***

The rate of development of 3TC resistance is approximately 20% per year among HIV/HBV-co-infected persons treated with 3TC. In HIV-infected patients who have been on 3TC and are currently candidates for treatment of chronic HBV, some experts recommend use of adefovir or TDF. How long 3TC should be continued beyond initiation of a new treatment is unknown.

For HIV-infected persons previously treated with a 3TC-containing HAART regimen, uncontrolled data suggest that the combination of adefovir with continued 3TC has substantial antiviral effects even in the presence of 3TC resistant HBV. Many experts would use adefovir to treat chronic HBV in HIV-infected patients who have had an inadequate response to a course of 3TC therapy as evidenced by high plasma HBV DNA levels or persistent serum HBeAg. Whether 3TC should be continued (or restarted) if not needed as part of the ARV regimen is unknown.

Although there are sparse data and the drug is not approved for this indication, some experts would recommend TDF to treat chronic HBV in HIV-infected patients who require HAART

and remain HBeAg positive or have high levels of circulating HBV DNA despite twelve or more months of 3TC. Whether 3TC should be used (or restarted) in such patients is unknown.

Flares of liver disease have been reported with development of resistance to 3TC. If this occurs, addition of TDF or adefovir may be life-saving. HBV DNA testing may be useful in this setting, since increasing levels are associated with emergence of 3TC resistance or relapse, while stable levels should suggest an alternative cause of acute deterioration.

ESLD in HBV- and HIV-co-infected patients is managed as it is in HIV-negative patients. Interferon is contra-indicated in ESLD, but limited data suggest that 3TC and adefovir can be safely used. Liver transplantation has been performed with limited success in selected patients with HBV and HIV infection. If a patient is thought to be a candidate for liver transplantation, early consultation with a transplant centre should be obtained because transplantation does not cure HBV infection and adequate posttransplant treatment is required.

#### ***Prevention of Relapse and Recurrence***

In HIV-negative, HBeAg-negative patients with chronic HBV who are treated with 3TC, ALT and HBV DNA levels may decline, but high rates of relapse have been reported when therapy is stopped. Thus, the optimal duration of treatment of HBeAg-negative patients, whether HIV-infected or not, is unknown. There are no known effective means to prevent recurrence or flares of chronic HBV.

#### ***Special Considerations in Pregnancy***

All pregnant women should be screened for HBsAg. Treatment of symptomatic acute HBV infection during pregnancy should be supportive with special attention given to maintaining blood glucose levels and normal clotting status. Risk of preterm labour and delivery may be increased with acute HBV infection.

Treatment of chronic HBV infection is generally not indicated in pregnancy. Hepatitis A vaccination, indicated for persons with chronic HBV infection, can be given during pregnancy.

Infants born to HBsAg-positive women should receive hepatitis B immune globulin and HBV vaccine within twelve hours of birth. The second and third doses of vaccine should be given at age one and six months, respectively. This regimen is 95% or more effective in preventing HBV infection in these infants. Post-vaccination testing for anti-HBs and HBsAg should be performed at age nine to fifteen months because of the infant's ongoing exposure to HBV.

If treatment for chronic HBV is necessary, 3TC is the preferred agent, as it has not been shown to be teratogenic in animals or based on human experience including over 1,000 first trimester exposures reported to the Antiretroviral Pregnancy Registry. 3TC should only be used in HIV-infected pregnant women as part of a fully suppressive HAART regimen.

Only limited information is available regarding adefovir. It is embryotoxic in mice and caused neonatal thymic lymphoid tissue destruction with use in later pregnancy in mice. No reports of its use in human pregnancy are available. Cases of exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry at (910) 256-0263, email: [registry@inveresk.com](mailto:registry@inveresk.com) or [www.APRegistry.com](http://www.APRegistry.com).

Limited information is available regarding TDF. No birth defects have been seen in studies of rats, rabbits, and monkeys. Decreased foetal weights and increased bone density were seen in monkeys after high-dose exposure *in utero*. Nineteen cases of first trimester exposure in humans without birth defects have been reported. Cases of exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry at (910) 256-0263, email: [registry@inveresk.com](mailto:registry@inveresk.com) or [www.APRegistry.com](http://www.APRegistry.com).

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