THERAPEUTIC GUIDELINES
FOR OPPORTUNISTIC INFECTIONS

As of May 2009
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1. PNEUMOCYSTIS JIROVECI PNEUMONIA (PJP)  
(formerly Pneumocystis carinii Pneumonia, PCP)

i) PROPHYLAXIS
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v) PJP IMMUNE RECONSTITUTION SYNDROME

i) PROPHYLAXIS

a) Indications:
   Primary prophylaxis is recommended for patients with any of the following  
   • CD4 count below 200/mm³
   • CD4 fraction below 14%
   • recurrent oral thrush
   • consider if CD4 < 250/mm³ and follow-up uncertain (JID 1998;178:1126-32)

Secondary prophylaxis:
   • any patient who has previously had an episode of PCP

   HIV-infected individuals should have monitoring every 1-2 months of their CD4  
   counts to identify the appropriate time to start PJP prophylaxis.

   Prior to starting PJP prophylaxis, patients should be assessed to confirm that  
   they do not have active pulmonary disease requiring specific therapy (i.e. PCP or  
   tuberculosis).

b) Prophylaxis Options:
   1. Trimethoprim-sulfamethoxazole (TMP-SMX) one double strength [DS] tablet  
      daily (160 mg trimethoprim - 800 mg sulfamethoxazole) is the recommended  
      (one single strength [SS] tablet daily or one DS tablet three days each week)  
      are better tolerated but slightly less effective (Arch Intern Med 1996;156:177).  
      TMP-SMX is the most effective of the available regimens. It also protects against  
      bacterial infections and Toxoplasma gondii.

   Adverse reactions include allergic reactions, cytopenias, increases in serum  
   creatinine, hyperkalemia, and gastrointestinal symptoms. Monitoring should  
   include CBC, differential, BUN, creatinine, and electrolytes. Patients should be  
   warned that allergic reactions are frequent, occurring in at least 30% of patients.
Allergic reactions are usually characterized by fever and/or an erythematous, pruritic rash. If an allergic reaction develops, the medication should be discontinued at once.

2. **Dapsone** 100 mg daily. Consider screening patients for G-6-PD deficiency and avoid dapsone if G-6-PD deficient. This regimen may be less effective than TMP-SMX. Dapsone does not provide prophylaxis for toxoplasmosis unless combined with pyrimethamine (see Toxoplasmosis).

   **Adverse reactions** include hemolytic anemia secondary to methemoglobinemia (associated with an elevation of LDH), thrombocytopenia, neutropenia, liver dysfunction, rash, gastrointestinal intolerance, and allergic reactions.

3. **Atovaquone** 1500 mg/day has similar efficacy for the prevention of PJP compared to dapsone or aerosol pentamidine (NEJM 1998;339:1889; JID 1999;180:369) and also provides prophylaxis for toxoplasmosis, but is very expensive (annual drug acquisition cost in British Columbia of atovaquone $8,942, TMP-SMX $95, dapsone $172, and aerosol penatmidine $600). Atovaquone must be taken with meals to ensure optimal absorption of the drug. Atovaquone can be obtained through the Centre for Excellence at 1-800-665-7677.

   **Adverse reactions** include headache, nausea, diarrhea, rash, and fever. These are generally mild to moderate.

4. **Aerosol pentamidine** 300 mg once monthly via a Respigard II nebulizer. Premedication with a Beta 2 agonist (Ventolin 2 puffs prn) is generally recommended.

   Aerosol pentamidine (AP) is relatively expensive and less convenient than the oral regimens of trimethoprim-sulfamethoxazole or dapsone as described above. Patients who develop PJP during aerosol pentamidine prophylaxis should be considered for subsequent higher prophylactic dose (300 mg twice monthly). Aerosol pentamidine is less effective than trimethoprim-sulfamethoxazole or dapsone, particularly in patients whose CD4 counts are <100/mm³ (NEJM 1995;332:693). In contrast to TMP-SMX, aerosol pentamidine does not provide any prophylaxis against toxoplasmosis or bacterial infections.

   **Adverse reactions**: Some patients develop bronchospasm. There is some evidence that the use of aerosol pentamidine may be associated with the development of atypical presentations of PJP including apical disease, pneumothoraces, and systemic pneumocystosis. Active pulmonary tuberculosis should be ruled out before initiating aerosol pentamidine.
5. **Other PJP prophylaxis alternatives:**

- First line treatment (induction or suppression) for toxoplasmosis with sulfadiazine (not with clindamycin) plus pyrimethamine provides adequate PJP prophylaxis (Ann Intern Med 1991;115:760).

- There is little published experience with pentamidine 4 mg/kg IV q2-4 weeks for prophylaxis.

c) **Discontinuing PJP prophylaxis.**

For patients who experience CD4 cell count recovery to ≥ 200 cells/mm³ for at least 3 months with continued combination antiretroviral therapy can discontinue either primary or secondary PJP prophylaxis (NEJM 1999;340:1301; NEJM 2001;344:168; NEJM 2001;344:159; Ann Intern Med 2002;137:435)

d) **Desensitization regimens for TMP-SMX allergy.**

Desensitization (J Allergy Clin Immunol 1998;102:1033) or dose escalation (JID 2001;184:992) for patients who have allergic reactions to sulfa drugs (trimethoprim-sulfamethoxazole or dapsone) have been proposed. However, this should only be undertaken after consulting an experienced specialist. The use of concomitant longterm prednisone for the suppression of sulfa drugs intolerance is not recommended.

ii) **TREATMENT**

a) **Indication:**

While a presumptive diagnosis of PJP on the basis of clinical, laboratory, and radiological findings can be made, a definite diagnosis of PJP is confirmed using bronchoalveolar lavage. Treatment should not be delayed while waiting for bronchoscopy results [may take several days] in suspected cases. Positive confirmation and management should be done in consultation with an experienced specialist.

An elevated lactic dehydrogenase level (LDH), although non-specific, is a characteristic feature of PJP. The degree of elevation of the LDH generally parallels the severity of the disease. Changes in the LDH level following initiation of treatment also correlate with the course of the disease [i.e., a positive response to therapy is indicated by a decrease in the LDH level]. Dapsone can lead to hemolysis which can increase the LDH level.

b) **Treatment options:**

The recommended treatment duration is 3 weeks.
AMBULATORY MANAGEMENT

Patients with mild to moderate PJP may be treated on an ambulatory basis. See the indications for intravenous therapy (below). This decision is based on the clinical status of the patient including the degree of dyspnea, oxygen saturation, as well as the ability to tolerate and comply with oral therapy. TMP-SMX is the preferred choice for the ambulatory treatment of AIDS-related PJP. If this regimen is not well tolerated, then dapsone/trimethoprim is a reasonable alternative. Atovaquone or clindamycin-primaquine should be reserved for those individuals who cannot tolerate TMP-SMX or dapsone/trimethoprim.

The preferred oral treatment options in descending order are as follows:

1. **Trimethoprim-sulfamethoxazole** (TMP-SMX) two double strength (DS) tablets every 8 hours (or same dose as for intravenous therapy, in 3 divided doses) for 21 days (Clin Infect Dis 2005;40:S131).

   **Adverse reactions:** allergic reactions, cytopenias, increases in serum creatinine, hyperkalemia, gastrointestinal symptoms, and occasionally hepatitis. Monitoring should include CBC, differential, liver enzymes, BUN, creatinine, and electrolytes.

2. **Dapsone** 100 mg orally once daily combined with **trimethoprim** 5 mg/kg three times daily for 21 days (NEJM 1990:323:776). Consider screening patients for G-6-PD deficiency and avoid dapsone if G-6-PD deficient.

   **Adverse reactions** include methemoglobinemia and hemolytic anemia (associated with an elevation of LDH), thrombocytopenia, neutropenia, liver dysfunction, rash, and gastrointestinal intolerance.

3. **Clindamycin** 300-450 mg orally four times daily combined with **primaquine** 15-30 mg (base) orally daily (Ann Intern Med 1996;124;792). Consider screening patients for G-6-PD deficiency and avoid primaquine if G-6-PD deficient.

   **Adverse reactions** include fever, rash, gastrointestinal intolerance, *C. difficile* colitis, methemoglobinemia, and hemolytic anemia (particularly in patients with G-6-PD deficiency).

4. **Atovaquone suspension**, 750 mg orally bid with meals for 21 days. Atovaquone should be taken with meals to ensure optimal absorption of the drug. Atovaquone treatment is associated with reduced survival compared to TMP-SMX (NEJM 1993;328:1521). Atovaquone can be obtained through the Centre for Excellence at 1-800-665-7677.

   **Adverse reactions** are generally mild to moderate and include: headache, nausea, diarrhea, rash, and fever.
INTRAVENOUS TREATMENT
The ambulatory treatments discussed above can be used effectively in hospitalized patients with mild to moderate disease. Intravenous therapy is indicated if any of the following are present:

- gastrointestinal intolerance (e.g. vomiting, severe esophagitis) or malabsorption
- borderline respiratory status (e.g. \( \text{pO}_2 < 70 \text{ mm Hg} \), or \( \text{A-a gradient} > 45 \text{ mm Hg} \))

Note that patients should be changed to an oral regimen (to complete 21 days of therapy) as soon as there is clinical improvement and it can be tolerated. If intravenous therapy is required the following treatment options are as follows in descending order:

1. **Trimethoprim** (15 mg/kg/day) - **sulfamethoxazole** (75 mg/kg/day) divided q6-8h.
   - **Adverse reactions** include allergic reactions (including Stevens-Johnson syndrome), cytopenias, increases in serum creatinine, hyperkalemia, hepatitis and gastrointestinal symptoms. Monitoring should include CBC, differential, liver enzymes, BUN, creatinine, and electrolytes.

2. **Clindamycin** 600-900 mg intravenously every 6-8 hours plus primaquine 15-30 mg orally daily. Consider screening patients for G-6-PD deficiency and avoid *primaquine* if G-6-PD deficient.
   - **Adverse reactions** include fever, rash, gastrointestinal intolerance, *C. difficile* colitis, methemoglobinemia, and hemolytic anemia (particularly in patients with G-6-PD deficiency).

3. **Pentamidine isethionate** 4 mg/kg/day over 1-3 hours for five days, followed by 3 mg/kg/day to complete therapy (Ann Intern Med 1986;105:37. AIDS 1992;6:301).
   - **Adverse reactions** include renal and liver dysfunction, neutropenia, thrombocytopenia, hyponatremia, rash, fever, and gastrointestinal upset. Hypotension, at times severe, can be reduced by administering the drug slowly over several hours. Hypo- and hyperglycemia, cardiac rhythm disturbances, and pancreatitis are uncommon but potentially serious. Due to the increased risk for pancreatitis, didanosine should not be used concomitantly with systemic pentamidine, and should only be restarted a few weeks after stopping parenteral pentamidine.
iii) ADJUNCTIVE PREDNISONE THERAPY

Prednisone is recommended for the treatment of patients with moderate to severe AIDS-related PJP as defined by pO₂ less than 70 mmHg, arterial-alveolar O₂ gradient > 35 mmHg, or O₂ saturation of < 90% while breathing room air [NEJM 1990;323:1500. Ann Intern Med 1990;113:14].

Prednisone should be started 15-30 min before TMP-SMX. The dose of prednisone is 40 mg bid for 5 days, then 40 mg/day for 5 days, then 20 mg/day for 11 days (21 days total). Prednisone therapy should be continued until discontinuation of the antimicrobial therapy. Early discontinuation of prednisone therapy has been associated with rebound of signs and symptoms. Prednisone has been shown to reduce mortality and morbidity in acute moderate to severe PJP.

iv) TREATMENT FAILURE

Patients may worsen clinically during the first 2-3 days of treatment but usually are improving by about the 5th day. Failed therapy is defined as lack of improvement or worsening lung function (on arterial blood gases) after 4-8 days of therapy. Aside from lack of efficacy of the anti-pneumocystis regimen, other considerations include: pneumothorax, fluid overload, co-existing respiratory tract infection, and ARDS. In the absence of controlled trials, a meta-analysis of salvage therapy suggested that clindamycin plus primaquine was the most effective alternative to the initially prescribed regimen [Arch Intern Med 2001;161:1529]. Consultation with an experienced physician is recommended in this situation.

v) PJP IMMUNE RECONSTITUTION SYNDROME

Initiation of antiretroviral therapy [ART] during therapy for PJP has been associated with a paradoxical worsening of the pulmonary infiltrates and lung function in up to 5-18% of cases [Am J Resp Crit Care Med 2002;165:1670]. In most cases of PJP immune reconstitution syndrome [PJP-IRS] the clinical deterioration has been observed during the first month after starting ART. The diagnosis is supported by bronchoscopy with transbronchial biopsy in order to exclude other possible causes; however, there may be few or no demonstrable PJP organisms [CID 2002;35:491]. Any diagnosis of IRS should be supported by evidence of a virologic [HIV RNA reduction of ≥ 1 log₁₀] and/or immunologic [CD4 increase] response to the ART regimen. Some patients with PJP-IRS have developed respiratory failure and appeared to respond to systemic corticosteroids and/or ART interruption [AM J Resp Crit Care Med 2001;165:847]. Although controversial, it may be advisable to postpone ART until PJP.
treatment has been completed. However, two retrospective studies have suggested a survival benefit associated with initiating concurrent ART during PCP therapy [JID 2001;183:1409. AIDS 2003;17:73]. These two studies are limited by their retrospective design. A recent recommendation is to postpone ART until there has been a response to PJP therapy [CID 2005;40:S131].
Toxoplasma serology should be done at the baseline work-up of HIV-infected patients. While positive serology identifies those at greater risk, up to 16% of those presenting with CNS toxoplasmosis will have negative serum serology (NEJM 1992;327:1643). Toxoplasma encephalitis is the most frequent clinical manifestation of disease in HIV-infected patients. Seroprevalence of T. gondii in North American adults is approximately 10-20%. Among HIV-positive/T. gondii infected (i.e. toxoplasma IgG antibody positive) adults not receiving prophylaxis and with CD4 counts of < 100 cells/mm³, the probability of developing clinical toxoplasmosis is approximately 38%.

i) PROPHYLAXIS

Indications for prophylaxis:

- **Primary prophylaxis:** Patients having both positive toxoplasma IgG serology and a CD4 count < 100 cells/mm³.

- **Secondary prophylaxis:** Any patient with a previous diagnosis of toxoplasmosis.

a) Prophylactic Treatment Options

**PRIMARY PROPHYLAXIS:**

- **TMP-SMX** (trimethoprim-sulfamethoxazole) 1 double-strength (DS) tablet daily (Ann Intern Med 2002;137:435)

- **Alternative Regimens** (if intolerant to TMP-SMX 1 DS tablet daily) in descending order of preference:
  
  » **TMP-SMX** 1 single-strength (SS) tablet daily

  OR

  » **Dapsone** 50 mg daily (or 100 mg daily) **plus pyrimethamine** 50 mg/week **plus leukovorin** (folinic acid) 25 mg/week

  OR

  » **Atovaquone** solution 1500 mg/day (plus/minus **pyrimethamine** 25 mg/day plus **leukovorin** 10 mg/day)

- **Sulfadiazine** 500-1000 mg orally four times daily (available through Health Protection Branch, see Induction Therapy below) plus **pyrimethamine** 25-50 mg/day orally plus **leukovorin** 10-25 mg/day

- **Alternative Regimens**
  - **Clindamycin** 300 mg every 6 hours or 450 mg every 8 hours plus **pyrimethamine** 25-50 mg/day plus **leukovorin** 10-25 mg/day. Clindamycin/pyrimethamine is associated with a higher relapse rate compared to sulfadiazine/pyrimethamine (Clin Infect Dis 1996;22:268) and does not provide adequate PCP prophylaxis (Lancet 1989;1:1459)
  - **Atovaquone** 750 mg PO q6-12h with or without **pyrimethamine** 25 mg/day plus **leukovorin** 10 mg/day (AIDS 1996;10:1107)
  - **TMP-SMX** 2.5 mg/kg PO BID (approximately 1 DS tab BID if body weight ~70 kg) (AAC 1998;42:1346)

b) Discontinuing Toxoplasmosis Prophylaxis

- **Primary prophylaxis** may be discontinued for patients who experience HAART-induced immune reconstitution associated with an increase in the CD4 count to > 200/mm³ for at least 3 months. Primary prophylaxis should be restarted if the CD4 count falls to < 100-200/mm³ (Ann Intern Med 2002;137:435).

- **Secondary toxoplasmosis prophylaxis.** This may be considered for patients who have no signs and symptoms of toxoplasma encephalitis and have responded well to HAART, with sustained increases in CD4 counts to > 200/mm³ for ≥ 6 months. In this situation, the risk of relapse appears to be very low, although only a small number of such patients have been studied. Maintenance therapy should be restarted if the CD4 falls to < 200/mm³ (Ann Intern Med 2002;137:435. Clin Infect Dis 2002;34:662).
ii) TREATMENT

a) Empiric Therapy

**Indication for Empiric Therapy:**

Patients who meet all of the following criteria should be treated.

1. HIV infection and significant immune deficiency (CD4 count < 300 cells/mm³)

2. Compatible clinical presentation (usually including more than one of the following):
   - headaches
   - fever
   - seizures
   - focal neurologic deficit (e.g. hemiparesis, aphasia, ataxia)
   - cognitive impairment (e.g. confusion, reduced consciousness, coma)

3. Evidence of mass lesion on CT or MRI compatible with toxoplasmosis

Evaluating response to empiric therapy. An MRI (or CT) should be repeated after 2 weeks (or earlier if there is no clinical response). Patients worsening by day 7 or not responding clinically by day 10 of a trial of empiric therapy should be considered for stereotactic brain biopsy. A clinical and radiologic response confirms the diagnosis and warrants indefinite maintenance therapy. The absence of a response warrants additional investigation. Empiric therapy for toxoplasmosis should not be discontinued on the basis of negative serum toxoplasma serology (NEJM 1992;327:1643), atypical imaging findings (CT, MRI, or thallium SPECT scan), or a slow/delayed response. Empiric therapy should be continued until an alternate diagnosis has been established by stereotactic brain biopsy. If serum serology for *T. gondii* (IgG antibodies) is negative it argues against the diagnosis, although does not reliably exclude it. Primary central nervous system lymphoma (PCNSL) is the main differential diagnosis and is supported by a positive PCR for Epstein-Barr virus in the spinal fluid (if lumbar puncture is considered to be safe to perform). However a diagnosis of PCNSL is only reliably established by brain biopsy. Increased uptake of thallium-201 on brain SPECT (single-photon emission computed tomography) scan is evidence supporting a diagnosis of CNS malignancy such as PCNSL. Toxoplasmosis is not associated with increased uptake on brain SPECT scan.

**Role of corticosteroids.** Corticosteroids (e.g. dexamethasone) should only be used if there is evidence of life-threatening mass effect during a trial of empiric therapy for toxoplasmosis. The drawbacks to corticosteroids in this
setting include the usual potential adverse effects but more importantly the confounding effect on the evaluation of the response to toxoplasmosis therapy, since corticosteroids are associated with clinical improvement of PCNSL. Furthermore, if the patient proceeds to brain biopsy, the diagnostic yield on histopathology is reduced by corticosteroid use.

b) Treatment Options:

Treatment consists of induction therapy for 6 weeks, or possibly longer if there has been an incomplete response. This is followed by maintenance therapy indefinitely or until the patient meets criteria for stopping maintenance therapy (see Discontinuing Toxoplasmosis Prophylaxis above).

**INDUCTION THERAPY**

- **Sulfadiazine** 1000 mg (< 60 kg) to 1500 mg (> 60 kg) orally q6h (currently only available as compassionate release through Health Protection Branch ph 613-941-2108) [Clin Infect Dis 2005;40:S131].

  OR

- **Clindamycin** 600-900 mg IV q6h plus **pyrimethamine** 200 mg loading dose, then 50mg (< 60 kg body weight) to 75 mg (> 60 kg)/day orally plus **leukovorin** 10-20 mg/day for the first 3 weeks (or until there is a clinical response); then clindamycin orally 300 mg qid (or 450 mg tid) plus **pyrimethamine plus leukovorin** as above [Clin Infect Dis 2005;40:S131. Ann Intern Med 1992:116:33. Clin Infect Dis 1996;22:268].

  OR

- **Other induction therapy options** (expert advice should be sought before contemplating treatment with these agents)

  - **TMP-SMX** 5 mg/kg (approximately 2 DS tablets if body weight ~70 kg) IV or PO q12h [AAC 1998;42:1346]

    OR

  - **Atovaquone** 1500 mg PO BID with meals plus **pyrimethamine** 200 mg loading dose, then 50mg (< 60 kg body weight) to 75 mg (> 60 kg)/day orally plus **leukovorin** 10-20 mg/day [Clin Infect Dis 2002;34:1243]

    OR

  - **Azithromycin** 900-1200 mg PO daily plus **pyrimethamine** 200 mg loading dose, then 50mg (< 60 kg body weight) to 75 mg (> 60 kg)/day orally plus leukovorin 10-20 mg/day [AIDS 2001;15:583]

**MAINTENANCE THERAPY** (see Secondary Prophylaxis above)
iii) ADVERSE DRUG EFFECTS (ADE) AND MONITORING

- **Pyrimethamine**: leukopenia, thrombocytopenia, megaloblastic anemia, hypersensitivity, GI distress, and headaches. Cytopenias are mostly preventable by the addition of folinic acid, which is expensive and may not be necessary for all patients. **Leukovorin** dose adjustment should be made according to the results of monitoring blood counts [e.g. neutrophils, platelets].

- **Sulfadiazine**: cutaneous hypersensitivity, fever, leukopenia, crystalluria, GI upset, headache; less frequently, serum sickness, and rarely Stevens-Johnson syndrome. Adequate hydration reduces renal toxicity. Teratogenicity is a possibility, but experience is limited in pregnant women.

- **Clindamycin**: rash, gastrointestinal intolerance, fever, and *C. difficile* colitis

- **Zidovudine** (AZT)-containing antiretroviral regimens should be discontinued or modified during induction treatment if cytopenias are present, and restarted when counts allow and the pyrimethamine dose is reduced. Alternatively, neutropenia can be managed with G-CSF.

- **Monitoring**: BUN and creatinine: 2 times per week during induction therapy with sulfadiazine. CBC: during prophylaxis, every 2 weeks for the first 2 months, then every 1-2 months. During induction treatment, 2-3 times per week; during maintenance weekly, then monthly when counts are stable.
3. CRYPTOSPORIDIOSIS AND MICROSPORIDIOSIS

i) CRYPTOSPORIDIOSIS

a) Diagnosis.

Patients may present with acute or chronic profuse watery diarrhea. Severe and persistent disease is associated with advanced HIV disease and CD4 counts < 100/µL [Ann Intern Med 1992;116:840], and in 10-30% of patients may involve the biliary tract resulting in AIDS cholangiopathy. The diagnosis is established by microscopic identification of the oocysts of Cryptosporidium species in stool samples (modified acid fast stain or immunofluorescence) or in the brush border of small intestinal biopsies.

b) Treatment.

- **HAART** should be initiated (or revised if on a failing regimen) and has been associated with resolution of cryptosporidiosis [Lancet 1998;351:256].

- **Supportive care.** Fluid and electrolyte replacement should be provided orally or intravenously as needed. Antimotility agents (e.g. loperamide) may be helpful. Occasional patients require total parenteral nutrition.

- **Antiparasitic drugs.** No reliably effective antiparasitic drug has been identified for HIV-related disease [Clin Infect Dis 2005;40:S131]. As a result, management should focus on HAART and supportive care as above. For those who do not respond, use of one of the following drugs might be considered. **Nitazoxanide** (500 mg PO BID) has efficacy in HIV-negative patients, but was not associated with improved outcomes in HIV-related cryptosporidiosis in one study [Lancet 2002;360:1375], or when the CD4 was < 50/µL in another [Trans R Soc Trop Med Hyg 1998;92:663]. **Paromomycin** (1 gm PO BID or 500 mg QID), a non-absorbable aminoglycoside has been studied in two small randomized trials of HIV-related cryptosporidiosis, only one of which demonstrated clinical benefit [J Infect Dis 1994;170:419. Clin Infect Dis 2000;31:1084]. A small open-label study suggested clinical benefit with the combination of paromomycins plus **azithromycin** (600 mg PO daily) [J Infect Dis 1998;178:900]. Numerous other drugs have been studied but have even less evidence to support their use in this situation.

ii) MICROSPORIDIOSIS

a) Diagnosis

b) Treatment
ii) MICROSPORIDIOSIS

a) Diagnosis. The most common species of microsporidia (protists related to fungi) to cause human disease are Enterocytozoon bieneusi and Encephalitozoon species; they both cause intestinal and biliary disease similar to cryptosporidiosis. However the latter also having the ability to cause disseminated disease. Most symptomatic disease occurs in HIV positive patients with CD4 counts < 100/µL (Clin Infect Dis 1995;21 Suppl 1:S62). The diagnosis is established by the microscopic demonstration of the spores in stool (e.g. modified trichrome stain) or tissue biopsy (e.g. intestinal biopsy for light and electron microscopy [EM]). EM is needed for species identification (Clin Microbiol Rev 1994;7:426).

b) Treatment.

- **HAART** should be initiated [or revised if on a failing regimen] and has been associated with resolution of microsporidiosis [AIDS 1997;11:1658].

- **Supportive care.** Fluid and electrolyte replacement should be provided orally or intravenously as needed. Antimotility agents [e.g. loperamide] may be helpful. Occasional patients require total parenteral nutrition.

- **Antiparasitic drugs:** for intestinal, ocular, and disseminated disease the drug of choice is albendazole [a tubulin inhibitor] 400 mg PO BID x 3 weeks [J Infect Dis 1998;177:1373]. Enterocytozoon bieneusi is less susceptible to albendazole, but may respond to fumagillin 20 mg PO BID [not available in North America]. Fumagillin eye drops are also recommended for ocular infections [Leiter’s Pharmacy, San Jose, CA 1-800-292-6773].
4. CANDIDIASIS

i) OROPHARYNGEAL CANDIDIASIS
   a) Prophylaxis
   b) Treatment

ii) ESOPHAGEAL CANDIDIASIS
   a) Prophylaxis
   b) Treatment

iii) VAGINAL CANDIDIASIS

iv) AZOLE-REFRACTORY ORAL AND ESOPHAGEAL CANDIDIASIS

4. CANDIDIASIS

i) OROPHARYNGEAL CANDIDIASIS (Thrush)

HIV positive patients with thrush should be considered for PJP prophylaxis, even if the CD4 count is greater than 200 cells/mm³.

a) Prophylaxis:

   Primary. Specific antifungal agents are not recommended for this purpose.

   Secondary (suppressive therapy). This is generally not recommended (Clin Infect Dis 2005;41:1481.) unless disease-free intervals between episodes are short (e.g. less than a month) and recurrent symptoms are associated with smear positive (Gram stain or KOH) lesions. Factors to be considered include frequency and severity of episodes, drug toxicities and interactions, and cost. However continuous and episodic fluconazole were associated with similar risk of developing fluconazole-refractory mucosal candidiasis (Clin Infect Dis 2005;41:1473). Treatment options include (Ann Intern Med 2004;38:161. Ann Intern Med 2002;137:435) the following:

   • fluconazole 100-200 mg daily

   OR

   • itraconazole oral solution [not capsules] 200 mg daily

   Note: Symptomatic episodes may occur more frequently and be more difficult to control with topical therapy in patients with marked CD4 lymphopenia.

b) Treatment:

   While topical agents generally are not as well tolerated and may be less effective than systemic therapy (CID 1997;24:1204; Antimicrob Ag Chemother 1990;34:2267), they are generally less expensive and free of potential drug interactions. Treatment duration is 7-14 days. Itraconazole has less reliable absorption and more drug interactions than fluconazole. Systemic therapy is preferable for moderate to severe or recurrent infection.
**SYSTEMIC THERAPY**


  OR

- **Itraconazole oral solution** [not capsules] 100-200 mg daily [Clin Infect Dis 1998;26:1368.

  OR

**TOPICAL THERAPY** [Clin Infect Dis 2004;38:161]

- **Clotrimazole troches** (10 mg) dissolved in the mouth and swallowed 5 times/day (JAIDS 1993;6:1311)

  OR

- **Nystatin** suspension 200,000-400,000 units swish and swallow, 5 times/day

  OR

- **Amphotericin B** 1 ml (100 mg) or lozenges (10 mg) qid

**ii) ESOPHAGEAL CANDIDIASIS**

a) **Prophylaxis:** [See above Oropharyngeal candidiasis]

b) **Treatment:**

Immunocompromised HIV-positive patients with retrosternal dysphagia (particularly if associated with oral candidiasis) should be treated empirically for esophageal candidiasis. If there is no improvement after 5-7 days, endoscopy should be performed to establish a diagnosis. Patients with prominent odynophagia are more likely to have esophagitis due to other causes (e.g. CMV, HSV, or aphthous ulcer). A systemic antifungal is recommended for 2-3 weeks. Intravenous therapy is indicated for those who are unable to swallow. Treatment options include [Clin Infect Dis 2004;38:161]:

- **Fluconazole** 100-200 mg orally daily [Ann Intern Med 1992;117:655].

  OR

- **Itraconazole oral solution** [not capsules] 200 mg daily [JID 1997;176:227]
iii) VAGINAL CANDIDIASIS

a) Prophylaxis: [See above Oropharyngeal candidiasis]

b) Treatment:

Treatment duration is ≥ 7 days for disease that is severe, recurrent, involving non-albicans species, or in abnormal hosts such as HIV-positive women (Clin Infect Dis 2004;38:161). Systemic therapy is recommended for patients who do not tolerate or respond to topical therapy.

**TOPICAL THERAPY:**
- topical “over the counter” (OTC) azole (clotrimazole or miconazole), or by prescription (terconazole or butoconazole). Azoles may be unreliable for non-albicans species, which may respond to boric acid 600 mg gelatin capsule intravaginally x 14 days.

OR
- nystatin 100,000 units/day x 7-14 days

**SYSTEMIC THERAPY:**
- Fluconazole 150 mg and repeat 72 hours later

OR
- Itraconazole 200 mg daily x 7 days

iv) AZOLE-REFRACTORY ORAL AND ESOPHAGEAL CANDIDIASIS

Resistant strains of Candida species may occur in severely immunosuppressed patients who have received prolonged azole therapy. Azole-refractory cases should have a smear [gram stain or KOH] confirmation of the diagnosis of thrush and a throat culture collected. Treatment options include the following (oral amphotericin B and nystatin are not recommended for esophageal candidiasis):

- Itraconazole oral solution 100 mg bid x 2 wks, then 3 days/wk, [AIDS 1996;10:1369], or
- Amphotericin B oral suspension [aqueous suspension] 1 ml [100 mg] swish and swallow [S&S] qid [between meals], or prepared from IV formulation: 5 ml [1 mg in D5W, with cherry syrup] S&S qid [Clin Infect Dis 1998;26:556], or
- Nystatin oral tablets [500,000 units] dissolved in the mouth and swallowed or suspension [0.5-1.0 million units] swished and swallowed, 3-5 times a day, or
Voriconazole 200 mg bid (AIDS 1998;12:2227), or

Caspofungin 50mg IV daily (JAIDS 2002;31:183), or

Amphotericin B 0.3-0.6 mg/kg IV daily

**SPECIAL CONSIDERATIONS:**

**Itraconazole oral solution** (not capsules) is recommended for oral and esophageal candidiasis. It is best absorbed when taken fasting (1/2-hr before a meal). There may be inadequate absorption in patients who have achlorhydria, treatment with inhibitors of gastric acid secretion, or antacid-containing drugs (e.g. ddl buffered tablets or liquid). If itraconazole is to be used during ddl treatment, administration of the two drugs should be separated by a few hours. Itraconazole increases the systemic exposure to the protease inhibitors, and a dose reduction may be indicated for indinavir to 600 mg q8h (instead of 800 mg q8h). Itraconazole metabolism is enhanced by certain drugs (e.g. rifampin, carbamazepine, phenytoin). Concomitant use of such drugs often results in failure of azole therapy.
## 5. CRYPTOCOCCOSIS

### i) PROPHYLAXIS

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### ii) TREATMENT

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### iii) CRYPTOCOCCAL IMMUNE RECONSTITUTION SYNDROME (IRS)

### i) PROPHYLAXIS:

#### a) Primary Prophylaxis

Both fluconazole and itraconazole have been shown to reduce the frequency of cryptococcal disease in HIV-infected patients. However, primary antifungal prophylaxis is not recommended because of the low frequency of disease, lack of survival benefit, potential for development of drug resistance, and cost (Ann Intern Med 2002;137:435).

#### b) Secondary Prophylaxis (Maintenance Therapy). Indicated for any patient who has recovered from a documented episode of cryptococcosis to prevent relapse. In the absence of secondary prophylaxis, the relapse rate at 1 year for HIV-related cryptococcal meningitis is approximately 50% in the pre-HAART era.

**PREFERRED REGIMEN**

- **Fluconazole** 200-400 mg orally daily indefinitely (Clin Infect Dis 2000;30:710) or until there has been adequate immune reconstitution to allow discontinuation of prophylaxis (see below).

**ALTERNATIVE SECONDARY PROPHYLACTIC REGIMENS**

[Clin Infect Dis 2000;30:710] are generally discouraged because of reduced efficacy and/or tolerance.

**OPTIONS INCLUDE:**

- **Itraconazole** 200 mg orally bid

OR

- **Amphotericin B** 1 mg/kg IV 1-3 times per week

Note: Drug interactions which may result in failed itraconazole therapy relate to reduced absorption or enhanced metabolism of itraconazole. Absorption is reduced by antacids or inhibitors of gastric acid secretion while enhanced metabolism by drugs such as rifampin, carbamazepine, and phenytoin results in ineffective itraconazole therapy.
c) **Discontinuing secondary prophylaxis for cryptococcosis.** Patients who have successfully completed initial therapy for cryptococcosis, have no signs or symptoms of cryptococcosis, and have sustained immunologic response to antiretroviral therapy with CD4 counts > 100-200 cells/mm³ for ≥ 6 months may be evaluated for stopping fluconazole suppressive therapy. Consideration should be given to repeating the spinal fluid examination before stopping fluconazole to determine if the cerebrospinal fluid is culture-negative and antigen-negative [Ann Intern Med 2002;137:435], particularly if the serum cryptococcal antigen remains positive. Patients who stop fluconazole suppressive therapy should be advised of the possibility of relapse and the need to report symptoms promptly.

ii) **TREATMENT**

Systemic antifungal treatment is indicated for patients with any of the following conditions:

- **Cryptococcal meningitis** documented by a positive cerebrospinal fluid (CSF) test using either antigen detection (latex agglutination) or culture. Note that low titres of cryptococcal antigen frequently persist in CSF following successful treatment in AIDS patients.

- **Non-meningeal sites of cryptococcal infection** (e.g. cryptococcemia, cutaneous, urinary tract, pulmonary, or other visceral involvement).

- **Positive serum cryptococcal antigen (titer > 1:8)** with or without evidence of clinical disease. No studies have been conducted in these patients and optimal therapy is unknown, however initial treatment with fluconazole or amphotericin B, followed by indefiniteazole suppressive therapy is recommended (CID 2000;30:710).

Spinal fluid examination: Unless contraindicated, all HIV-positive patients with cryptococcosis (any microbiologic evidence of disease such as a positive smear or culture from any site, or positive cryptococcal antigenemia) should have a spinal fluid examination to exclude meningitis, which may be asymptomatic.

a) **Cryptococcal Meningitis**

Amphotericin B is superior to fluconazole as initial therapy. This regimen is associated with improved survival and more rapid sterilization of CSF compared to fluconazole; however, adverse effects are more frequent [Ann Intern Med 1990;113:18. N Engl J Med 1997;337:15-21. Lancet 2004;363:1764-67].

**RECOMMENDED TREATMENT:**

**Step 1. Amphotericin B 0.7-1.0 mg/kg/day IV plus 5-flucytosine 100 mg/kg/day po (divided q6h) for 2-3 weeks, until there is a clinical response (i.e. afebrile, alert, no**
headache, or indication of increased intracranial pressure) [CID 2000;30:710. NEJM 1997;337:15]. Intravenous saline (500-1000 ml) should be given prior to each dose of amphotericin B in order to reduce nephrotoxicity. Monitoring blood work should include CBC, differential, BUN, creatinine, electrolytes, and magnesium.

**ALTERNATIVE REGIMENS:**


b) **amphotericin B** 0.7 mg/kg/day IV monotherapy

c) **fluconazole** 800 mg/day IV or PO plus **5-flucytosine** 100 mg/kg/day PO divided q6h [Clin Infect Dis 1994;19:741] if liposomal amphotericin B is also associated with major toxicity.

**Step 2. Fluconazole** 400 mg/day orally or IV for at least 10 weeks. Itraconazole 200 mg twice daily may be an alternative, provided there is no concomitant rifampin, rifabutin, anti-seizure medications, achlorhydria, or suspected malabsorption.

**Step 3.** After initial treatment [steps 1 and 2], the dose of fluconazole may be lowered to 200 mg/day (or kept at 400 mg/day) and maintained indefinitely to prevent relapse (see Secondary prophylaxis below) or until there has been adequate immune reconstitution in order to allow discontinuation of prophylaxis (see above: Discontinuing secondary prophylaxis for cryptococcosis).

**Intracranial pressure management.** Opening pressure (OP) should be measured provided there are no contraindications to lumbar puncture (LP) [i.e. no intracranial mass lesions or shift on imaging]. The LP should be performed in the lateral position each time spinal fluid examinations are performed. If the OP is > 250 mm H2O, then treat with daily large volume (up to 30 ml) lumbar punctures with the aim of reducing the OP by approximately 50%. Consider ventriculoperitoneal shunting if pressures remain elevated [Clin Infect Dis 2000;30:47. Clin Infect Dis 2000;30:710. Clin Infect Dis 2005;40:480]. Acetazolamide and corticosteroids are not recommended in AIDS-related cryptococcal meningitis [Clin Infect Dis 2000;30:47. Clin Infect Dis 2005;40:5131].
b) Cryptococcosis without Central Nervous System Involvement

PULMONARY

1. Mild-moderate disease

Recommended Treatment:

- **fluconazole** 200-400 mg daily indefinitely [Clin Infect Dis 2000;30:710]; or
- **itraconazole** 200-400 mg daily indefinitely, or
- **fluconazole** 400 mg/day plus **5-flucytosine** 100 mg/kg/day (divided q6h)

2. Severe disease

Recommended Treatment:

- **amphotericin** B 0.7-1.0 mg/kg/day plus/minus **5-flucytosine** 100 mg/kg/day (divided q6h) until there has been a clinical response, then treat with fluconazole (or itraconazole)

- **Isolated cryptococemia or a positive serum cryptococcal antigen** [titer > 1:8] with or without evidence of clinical disease. No studies have been conducted in these patients and optimal therapy is unknown, however initial treatment with fluconazole or amphotericin B followed by indefinite azole (e.g. fluconazole 200 mg/day) suppressive therapy is recommended because of the tendency of such patients to subsequently develop culture proven cryptococcosis if untreated [Clin Infect Dis 2000;30:710].

**Maintenance treatment** for non meningeal cryptococcosis is recommended as for cryptococcal meningitis [see above: Secondary Prophylaxis].

iii) CRYPTOCOCCAL IMMUNE RECONSTITUTION SYNDROME (IRS).

This condition is characterized by a paradoxical clinical deterioration following the initiation of antiretroviral therapy (ART) in approximately one third of patients with a previous (usually recent) diagnosis of cryptococcosis [AIDS 2005;19:399]. It is more likely to occur in patients who are ART naïve, have higher initial CSF cryptococcal antigen titers, and begin ART within 30 days after the diagnosis of cryptococcosis [Clin Infect Dis 2005;40:1049]. Based upon these observations, it may be advisable to postpone ART initiation until patients with recently diagnosed cryptococcal meningitis have received at least a month of antifungal therapy, particularly those with high CSF antigen titers. Clinical manifestations may include recurrent culture-negative meningitis (often with a higher CSF pleocytosis), cryptococcomas, lymphadenitis, and pulmonary nodules or infiltrates. The diagnosis is usually established by the
demonstration of a virologic (> \(1 \log_{10}\) reduction in HIV RNA) and/or CD4 response to ART in a patient with a relapse of meningeal symptoms, but with culture-negative CSF (Clin Infect Dis 2005;40:1049). Anecdotal evidence suggests a role for anti-inflammatory treatment (e.g. high dose steroids) for severe CNS manifestations (AIDS 2005;19:1043), and raised intracranial pressure should be managed (as above). Occasional fatal cases have been reported (AIDS 2005;19:1043), and consideration should be given to stopping ART. There is no evidence to support the use of more aggressive antifungal therapy; however, while awaiting the repeat CSF culture result to exclude the possibility of a culture-positive relapse, re-induction therapy with amphotericin B plus 5-flucytosine should be considered.
6. MYCOBACTERIUM AVIUM COMPLEX (MAC)

i) PROPHYLAXIS

a) Primary MAC Prophylaxis:

Indication: MAC prophylaxis is recommended for patients with an absolute CD4 count of < 50 cells/mm³.

Before starting prophylaxis, the possibility of disseminated MAC infection should be excluded by clinical evaluation, which may include a mycobacterial blood culture. Patients who may be starting rifabutin for MAC prophylaxis should also be screened in order to exclude active tuberculosis, since rifabutin monotherapy would result in rifampin resistance of the M. tuberculosis.

PRIMARy PROPHYLAXIS RECOMMENDED:

- Azithromycin 1200 mg once weekly

ALTERNATIVE PROPHYLAXIS OPTIONS:

- Clarithromycin 500 mg twice daily (or 1000 mg XL once daily, slow release formulation), or
- Rifabutin 300 mg daily

EFFICACY CONSIDERATIONS:

MAC prophylaxis has been associated with a survival advantage [NEJM 1996;335:428] in the pre-HAART era. The incidence of disseminated MAC in patients randomized to rifabutin or azithromycin or both drugs was 15.3, 7.6, and 2.8 % in the pre-HAART era. However, combination prophylaxis [rifabutin plus azithromycin] is not recommended due to expense and increased toxicity. Azithromycin prevents disseminated MAC in patients with CD4 < 50 cells/mm³ [NEJM 1996;335:392; Clin Infect Dis 1998;26:611] but does not appear to prevent the development of MAC immune reconstitution syndrome [Clin Infect Dis 2002;34:371], which develops as an "unmasking" of subclinical disease in 3% of patients who initiate antiretroviral therapy with a CD4 count of < 100 cell/ mm³ [CID 2005;41:1483]. Bacterial respiratory tract infections are also reduced with azithromycin [NEJM 1996;335:392].
**Clarithromycin.** The main disadvantages of this regimen include the greater pill burden and that clarithromycin/azithromycin resistance is more likely to be present in cases of breakthrough MAC bacteremia compared to azithromycin prophylaxis (~29-58% vs. 0-11%) [NEJM 1996;335:384. NEJM 1996;35:392]. Bacterial respiratory tract infections are also reduced with clarithromycin [Clin Infect Dis 2001;32:1615].

**Rifabutin.** The main disadvantages of rifabutin include reduced efficacy and drug interactions. Patients receiving boosted protease inhibitor antiretroviral regimens should receive a lower rifabutin dose of 150 mg 3 times/week.

**Discontinuing Primary MAC Prophylaxis:** MAC prophylaxis can be safely discontinued in patients who have responded to HAART with increased CD4 counts to > 100 cells/mm³ for at least 3 months [NEJM 2000;342:1085; Ann Intern Med 2000;133;493]. Prophylaxis should be restarted if the CD4 count falls to < 50-100 cell/mm³ [Ann Intern Med 2002;137:435].

**b) Secondary MAC Prophylaxis.**

All patients with documented MAC disease should continue to receive combination MAC therapy lifelong (see below), unless they meet the criteria listed below for discontinuing therapy.

**Discontinuing Secondary MAC Prophylaxis:** Patients may be considered for stopping chronic suppressive therapy for MAC if they meet all of the following criteria [Clin Infect Dis 2005;40:S131. Ann Intern Med, 2002; 137:734-7):

- achieve antiretroviral therapy induced immune reconstitution with sustained (≥ 6 mo) increase in CD4 to > 100 cells/mm³, and
- complete ≥ 12 months of therapy for MAC, and
- remain free of signs or symptoms of MAC disease

MAC suppressive therapy (secondary prophylaxis) should be restarted if the CD4 count falls to < 100 cell/mm³.

**ii) TREATMENT**

**Indication:**

Patients in whom *M. avium* is recovered from tissue biopsy (e.g. bone marrow) or normally sterile body fluid (e.g. blood) have *M. avium* disease and require therapy.
Recommended Treatment:

**COMBINATION THERAPY USING:**
- **Clarithromycin** 500 mg twice daily [NEJM 1996;335:377] or 1000 mg XL once daily (slow release formulation)

  plus

- **Ethambutol** 15 mg/kg daily

  plus/minus

- **Rifabutin** 300 mg daily (dose adjusted as needed for drug interactions)

**ALTERNATIVE REGIMEN:**
- **Azithromycin** 500-600 mg daily [CID 2000;31:1245; CID 1998;27:1278] (for patients receiving atazanavir-containing ART regimens, azithromycin is recommended rather than clarithromycin due to a drug interaction)

  plus

- **Ethambutol** 15 mg/kg daily

  plus/minus

- **Rifabutin** 300 mg daily (dose adjusted as needed for drug interactions)

**EFFICACY CONSIDERATIONS REGARDING RIFABUTIN:**
Rifabutin (RFB) added to the combination of clarithromycin (CLA) and ethambutol (EMB) has been associated with a reduction in the development of *M. avium* macrolide resistance during long-term follow-up. The significance of this finding in the HAART era is uncertain. Also, improved microbiologic responses and survival were observed with the 3-drug regimen [CLA, EMB, plus RFB] compared to CLA plus EMB in one study [Clin Infect Dis 2003;37:1234], but not in a larger placebo-controlled trial [Clin Infect Dis 1999;28:1080].

**iii) MACROLIDE-RESISTANT MAC AND SECOND LINE DRUGS:**
Clarithromycin, ethambutol, and rifabutin are reasonably well-tolerated and have the greatest activity against MAC of the available antimicrobials. Results of in vitro susceptibility testing are predictive of therapeutic outcome with clarithromycin and azithromycin [Antimicrob Ag Chemother 1996;40:1759]; however, such clinical correlation studies are lacking for other drugs in the treatment of MAC, which makes interpretation of such results problematic. Consideration of alternative drugs in
a combination regimen should in general be limited to patients with documented macrolide-resistant MAC (clarithromycin MIC ≥ 32 µg/ml, or azithromycin MIC ≥ 256 µg/ml). Options are limited but include: ciprofloxacin 500-750 mg twice daily, or levofloxacin 500 mg daily. Moxifloxacin (400 mg daily) also appears to have activity against MAC (Antimicrob Ag Chemother 2001;45:217), although clinical trials are lacking. Other drugs which have demonstrated activity against MAC in animal studies but for which there is scant clinical evidence include linezolid, mefloquine, and the triple drug regimen of mefloquine, moxifloxacin, and ethambutol (J Infection 2002;44:201. J Infect Dis 2003;187:1977). Clarithromycin doses > 1 gm/day should be avoided since they are associated with reduced survival (Clin Infect Dis 1999;29:125).

A regimen for macrolide–resistant MAC may include the following drugs:

- a fluoroquinolone [e.g. ciprofloxacin, levofloxacin, or moxifloxacin], plus
- ethambutol, plus
- rifabutin

As for a number of other drug-resistant opportunistic infections, antiretroviral therapy (ART) is usually the most important intervention; and if there are problems related to drug interactions or polypharmacy, then ART should take priority over unproven and potentially toxic second line drugs. Other second line oral antimycobacterial drugs [ethionamide and cycloserine] may be associated with significant adverse effects, have uncertain efficacy, and are usually not recommended. Although clofazimine had been studied in MAC, it was associated with microbiologic failure and reduced survival in a randomized clinical trial [AIDS 1997;11:311]. Because of its potential toxicity, the need for vascular access, monitoring costs, and lack of proven efficacy, amikacin [10 mg/kg/day IV x 4 weeks] treatment is of doubtful value and was not associated with improved clinical or microbiologic outcomes in a randomized trial [AIDS 1998;12:2439]. Monotherapy with any drug is strongly discouraged because of the high likelihood of drug resistance developing.

iv) ADJUNCTIVE THERAPY

Patients who have persistent symptoms [e.g. fevers, fatigue, night sweats, weight loss] despite combination antimycobacterial therapy may benefit from a trial of corticosteroids [e.g. dexamethasone 2-4 mg daily] [Clin Infect Dis 1998;26:682. Antimicrob Ag Chemother 1994;38:2215].
v) MONITORING RESPONSE TO THERAPY AND DRUG TOXICITY.

Patients intolerant of, or not responding to the standard treatment after a 4 week trial should have a repeat MAC blood culture and be considered for the addition of another drug not included in the initial regimen, particularly if a 2-drug regimen is being used. Adjunctive corticosteroid should also be considered in this situation. If a blood culture remains positive at this point, then susceptibility testing with respect to clarithromycin/azithromycin may be considered. However macrolide resistance is rare during the first few months of therapy (Ann Intern Med 1994;121:905). If blood cultures have cleared but fevers continue then other causes of fever should be considered, including MAC immune reconstitution syndrome if an ART regimen has been started.

Drug toxicity.

- **Drug interactions.** Rifabutin results in significant drug interactions, most notably the need to reduce the rifabutin dose to 150 mg 3 times/week when co-administered with protease inhibitor-containing antiretroviral regimens. Clarithromycin is also associated with multiple drug interactions which need to be considered before initiating treatment.

- **Ethambutol ocular toxicity.** Baseline visual acuity (Snellen chart) and colour vision testing should be done for patients who will be receiving ethambutol (EMB). Patients should be questioned regarding visual symptoms at monthly follow-up visits, and those receiving an EMB dose of > 20 mg/kg/day or a duration of > 2 months should have monthly visual acuity and colour vision testing (Am J Respir Crit Care Med 2003;167:603, section 5.4).

- **Rifabutin** has been associated with uveitis (NEJM 1994;330:438), particularly when used in treatment regimens which include clarithromycin. Patients with ocular symptoms should be evaluated promptly by an ophthalmologist. If uveitis is suspected, rifabutin should be stopped immediately. Rifabutin may also cause pseudojaundice (normal bilirubin) and a polyarthralgia syndrome.

- **Clarithromycin** adverse effects include possible reduced hearing which is reversible.

vi) MAC IMMUNE RECONSTITUTION SYNDROME (MAC-IRS).

Among patients with disseminated MAC, initiation of antiretroviral therapy (ART) is associated with development of MAC-IRS in approximately 30% of cases (AIDS 2005;19:399). The clinical features of MAC-IRS most often include lymphadenitis, pulmonary-thoracic, or intraabdominal manifestations; however, any organ system may be involved (Clin Infect Dis 2005;41:1483). Patients who began ART within 30 days
(versus after 30 days) of initiating therapy for MAC had a relative risk of 2 for developing MAC-IRS. However, the optimal time to initiate ART in patients with disseminated MAC is unclear, and there have been no reported fatalities related to MAC-IRS. In contrast, the median survival in disseminated MAC with clarithromycin plus ethambutol plus rifabutin therapy in the pre-HAART era was only 8.7 months (NEJM 1996;335:377), suggesting that delays in starting ART should be minimized in MAC. It has been recommended that ART be initiated concurrently or within 1-2 weeks of starting MAC therapy (Clin Infect Dis 2005;40:S131).

Although there have been no controlled trials, the role of antimycobacterial therapy in MAC-IRS appears to be modest at best, and the addition of second line antimycobacterial drugs is not recommended (Clin Infect Dis 2005;41:1483). For patients with moderate to severe symptoms related to MAC-IRS, consideration should be given to a trial of NSAIDs or prednisone (20-40 mg/day for 4-8 weeks) (Clin Infect Dis 2005;40:S131). ART usually does not need to be interrupted.
7. TUBERCULOSIS

i) PROPHYLAXIS
   a) Indications
   b) Prophylaxis regimens

ii) RESPIRATORY ISOLATION

iii) NEWER DIAGNOSTIC TECHNIQUES

iv) TREATMENT
   a) Indications
   b) Antituberculosis regimen
   c) Follow-up evaluations and monitoring for drug-induced hepatotoxicity
   d) Concomitant antiretroviral therapy

iv) TUBERCULOSIS IMMUNE RECONSTITUTION SYNDROME

i) PROPHYLAXIS

The subsequent lifetime risk of developing active tuberculosis among those with latent tuberculous infection (i.e. positive tuberculin skin test [TST]; although TST will be negative in patients with anergy) is approximately 10% for HIV-negative [Am J Epidemiol 1974;99:131] compared to approximately 10% per year for HIV-positive patients. Therefore, all persons who are seropositive for HIV should be screened for tuberculosis including:

- review of the previous chest X-rays, TST results, and history of tuberculous disease or exposures
- TST using purified protein derivative (PPD) with 5 tuberculin units (5TU) by the Mantoux method. If the initial test was negative, consider repeating PPD test annually, and also repeat if there is a response to HAART with an increase in the CD4 count to > 200 cells/mm³, particularly in patients at high risk for exposure [Ann Intern Med 2002;137:435]. Routine anergy testing is not recommended [MMWR Recomm Rep 1997;46(RR-15):1-10]
- baseline chest x-ray is recommended in HIV-infected patients who are asymptomatic, which may be useful for detecting asymptomatic TB and also for comparison during the investigation of future respiratory symptoms [Clin Infect Dis 2004;39:609]. If clinical disease compatible with tuberculosis develops, then tuberculosis should be excluded regardless of the tuberculin status

a) Indications:
   Tuberculosis chemoprophylaxis is recommended (after excluding active tuberculosis) for any of the following circumstances [Ann Intern Med 2002;137:435. MMWR Recomm Rep 1998; 47:1]:
   a) a history of untreated or inadequately treated previous (inactive) tuberculosis
   b) previous or current tuberculin (PPD) reaction with induration of ≥ 5 mm in diameter, and no previous history of prophylaxis
   c) recent exposure to a documented infectious case of tuberculosis
Consultation with an experienced specialist is encouraged when the risk for tuberculosis is unclear.

b) Prophylaxis Regimen:

Isoniazid 5 mg/kg (maximum 300 mg/day) daily with pyridoxine 50 mg daily for 9 months [Ann Intern Med 2002;137:435]. Patients should be educated regarding the possible symptoms of INH hepatitis and to report them promptly.

ALTERNATIVE REGIMENS:

1. Isoniazid 900 mg plus pyridoxine 100 mg, both twice weekly for 9 months [preferably as directly observed therapy]. Patients should be educated regarding the possible symptoms of INH hepatitis and to report them promptly, or

2. Rifampin 10 mg/kg daily (maximum 600 mg/day) or rifabutin 300 mg daily for four months. Drug interactions, particularly involving antiretrovirals should be considered before initiating this regimen. This is the preferred regimen for contacts of patients with INH-resistant TB.

Pyrazinamide (PZA) plus either rifampin or rifabutin daily for 2 months is no longer recommended as a prophylactic regimen due to reports of fatal or severe hepatitis [MMWR 2003;52:735. CID 2006;42:346]

BCG. The use of bacille Calmette-Guerin (BCG) vaccine in HIV-infected patients is contraindicated because of the risk of developing disseminated disease [Ann Intern Med 2002;137:435].

Pyridoxine reduces the risk of isoniazid toxicity (e.g. peripheral neuropathy).

ii) RESPIRATORY ISOLATION

The limited number of negative-pressure respiratory isolation beds in many hospitals makes it difficult to comply [Arch Intern Med 1994;154:326] with the CDC (Atlanta, GA) guidelines which specify respiratory isolation for all HIV-positive patients with unexplained cough and fever pending the results of respiratory tract specimens for AFB smears [MMWR 2005;54[RR12]:1-81]. As a result, if there are insufficient isolation beds, then priority for isolation should be given to those most likely to have pulmonary TB, including those with: cavitary lesions, a miliary pattern, or hilar/mediastinal lymphadenopathy on chest x-ray; lack of response to empiric therapy for “bacterial pneumonia”; positive TST (and no history of TB treatment or prophylaxis); or additional risk factors for TB (e.g. history of TB or TB exposure, IDU, homeless, First Nations, or having been exposed to a high TB prevalence area).
iii) NEW DIAGNOSTIC TECHNIQUES.

Newer diagnostic techniques [e.g. RNA and DNA probes] may allow more rapid speciation which will facilitate respiratory infection control precautions and appropriate drug therapy. The direct application of these rapid detection methods to clinical specimens [rather than for the identification of organisms growing in culture] should be limited to respiratory tract specimens, for which they are approved. These rapid tests of respiratory specimens may be appropriate for some patients (e.g. sputum smear positive for acid fast bacilli [AFB] but associated with an intermediate to low pretest probability of tuberculosis; or sputum smear negative for AFB but associated with an intermediate to high pretest probability of tuberculosis) but not others (e.g. sputum smear positive for AFB and a high pretest probability; or sputum smear negative for AFB and a low pretest probability of tuberculosis [NEJM 1999;340:367]).

iv) TREATMENT

Tuberculosis is a reportable condition and should be managed in consultation with an experienced specialist.

a) Indications:

- **Confirmed mycobacterial infection.** Patients with a compatible clinical presentation and smear or culture positive for acid-fast bacilli recovered from clinical specimens [e.g. sputum, bronchoalveolar lavage or tissue biopsy], pending mycobacterial species identification. Occasional patients may have minimal symptoms [CID 2005;40:1500].

- **Presumed mycobacterial infection (empiric therapy).** Even when initial mycobacterial smears are negative, on the basis of careful clinical and radiologic evaluation, selected patients may be appropriate for empiric therapy. However, all relevant specimens for smear, culture, and rapid tests [RNA or DNA probes] should be obtained prior to initiating therapy. The identification of acid-fast bacilli in the appropriate setting should be considered to be M. tuberculosis, particularly in those with respiratory disease, lymphadenitis, or miliary disease. Tuberculosis can occur at any time during HIV disease, whereas infection with M. avium complex (MAC) usually occurs only in advanced disease [e.g. CD4 < 50-100 cells/mm³].

b) Antituberculous regimen:

Drug susceptibility assays will be routinely performed. Initial treatment of active tuberculosis is the same as for HIV-negative individuals and should include:
• Isoniazid 300 mg daily PLUS
• Rifampin 10 mg/kg daily [maximum 600 mg/day] PLUS
• Pyrazinamide 20-30 mg/kg daily PLUS
• Ethambutol 15-25 mg/kg/day PLUS
• Pyridoxine 25-50 mg daily

The above regimen should be continued daily for 2 months, followed by 4-7 months of isoniazid (and pyridoxine) and rifampin [Am J Respir Crit Care Med 2003;167:603] provided that the isolate is fully susceptible. Treatment should be longer for patients who have a slow clinical or bacteriologic response to therapy (i.e. continue for 6 months post-sputum conversion). There is some evidence of a higher relapse rate with short course 6-month regimens among HIV positive (0-10%) compared to HIV negative (0-3.4%) patients [CID 2001;32:623]. A 12-month treatment duration is recommended for those with skeletal or miliary tuberculosis [NEJM 1999;340:367]. Consultation is recommended for suspected or proven drug-resistant tuberculosis.

**Daily vs. intermittent therapy in the continuation phase of treatment.** If intermittent therapy is used, a thrice-weekly regimen with directly observed therapy (DOT) is recommended. Once weekly INH-rifapentine should not be used for HIV-infected patients. Twice weekly INH-rifampin (or INH-rifabutin) has been associated with increased rates of rifamycin resistance in HIV-infected patients and should be avoided, particularly among those with CD4 counts < 100/mm³ [MMWR 2002;51:214].

**Alternative regimens.** Rifabutin (300 mg daily) is associated with less prominent drug interactions than rifampin and may be used instead. However, non-rifamycin regimens should be avoided if possible, because they have been associated with reduced survival in HIV-infected patients [Tuber Lung Dis 1996;77:516].

**Previously treated tuberculosis, Multidrug-resistant TB (MDR-TB) and Extensively drug-resistant TB (XDR-TB).** Due to concerns related to drug resistance, two drugs to which the patient has not been previously exposed should be added. Directly observed therapy (DOT) should be considered for those with poor compliance. Drug interactions may complicate therapy. Upon completion of treatment, patients should be followed every 6 months for 2 years. Suspected or confirmed MDR-TB or XDR-TB should be referred immediately to an appropriate specialist. MDR-TB is defined as resistance to INH and rifampin. Recently, reports mainly from South Africa have drawn attention to the problem of XDR-TB defined as resistance to INH, rifampin, a quinolone, and at least one of the injectable drugs (capreomycin, kanamycin, or amikacin) [Lancet 2006;368:1575].
c) **Follow-up evaluations and monitoring for drug-induced toxicity.**

- **Follow-up evaluations.** Patients should be reassessed at least monthly to determine adherence, tolerance, and response to treatment. For those who were initially smear-positive, follow-up smears should be done at 2-week intervals until 2 consecutive specimens are negative. Follow-up chest x-ray is recommended after 2 months to evaluate response to treatment, and also at completion of treatment to provide a baseline for subsequent comparisons (Am J Respir Crit Care Med 2003;167:603, section 5.4).

- **Hepatotoxicity.** Pre-treatment evaluation of general health and liver function is required (e.g. INR, bilirubin, ALT, AST, LDH, alkaline phosphatase) and patients must be warned of the signs and symptoms of INH hepatitis and advised to report such symptoms promptly. Patients at increased risk of drug-induced hepatitis (i.e. age > 35, chronic liver disease, or daily alcohol intake) should have liver enzymes monitored monthly; whereas those who are not at increased risk should have liver enzymes done at baseline, at one month, and subsequently if previous tests were abnormal or if symptoms develop. Treatment should be discontinued if either the transaminase is > 5x the upper limit of normal (with or without symptoms), or if symptoms develop which are compatible with drug-induced hepatitis and transaminase > 3x the upper limit of normal [For details of managing hepatitis and other antituberculous drug toxicities see Am J Respir Crit Care Med 2003;167:603, section 6.3, page 636].

- **Ocular toxicity.** Baseline visual acuity (eye chart) and colour vision testing should be done for patients who will be receiving ethambutol (EMB). Patients should be questioned regarding visual symptoms at monthly follow-up visits, and those receiving an EMB dose of > 20 mg/kg/day or a duration of > 2 months should have monthly visual acuity and colour vision testing (Am J Respir Crit Care Med 2003;167:603, section 5.4).

d) **Concomitant Antiretroviral Therapy (ART).**

Consultation is recommended for treatment of both tuberculosis and HIV infection.

- **Timing.** Patients with TB/HIV co-infection and CD4 counts > ~200 cells/mm³ usually do not require antiretroviral therapy until the tuberculosis treatment has been completed. However, those with more advanced disease (CD4 < 200/mm³) should receive treatment for both infections. Due to overlapping toxicities, polypharmacy, and possible immune reconstitution syndrome, it has been recommended that ART be delayed for 4-8 weeks after the initiation of antituberculous therapy (Am J Resp Crit Care Med 2003;167:603). However, the high rate of AIDS events and death...
during the 8 week induction phase of antituberculous therapy among patients with CD4 counts < 100/mm³ [J Infect Dis 2004;190:1670] argues for earlier initiation of ART after the first few weeks, as soon as there as been a clinical response to antituberculous therapy. The main options are listed below and are largely determined by the drug interactions.

**Drug interactions.** There are numerous drug interactions involving mainly the rifamycins, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors [NNRTIs], but not the nucleoside reverse transcriptase inhibitors [NRTIs] [Am J Respir Crit Care Med 2003;167:603]. The clinical and pharmacokinetic studies supporting the following TB + ART regimens are cited below.

<table>
<thead>
<tr>
<th>TB regimen</th>
<th>ART regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a) Rifabutin-based</strong></td>
<td></td>
</tr>
<tr>
<td>• 150 mg 3x/wk</td>
<td>2-NRTIs + dual boosted protease inhibitor [Clin Infect Dis 2000;30:779. AIDS Clinical Care 2000;12:91-95], or</td>
</tr>
<tr>
<td>• 450-600 mg/day</td>
<td>2-NRTIs + efavirenz 600 mg/day [Am J Resp Crit Care Med 2003;167 :603. Clin Infect Dis 2005;41:1343]</td>
</tr>
<tr>
<td>• 300 mg/day</td>
<td>2-NRTIs + nevirapine 200 mg/d x 14d, then 200mg BID [Am J Respir Crit Care Med 2001;164:7]</td>
</tr>
<tr>
<td><strong>b) Rifampin-based</strong></td>
<td></td>
</tr>
<tr>
<td>• 600 mg/day</td>
<td>2-NRTIs + efavirenz 600 mg/day [AIDS 2005;19:1481. AIDS 2005;19:1541], or</td>
</tr>
</tbody>
</table>

See the following CDC website for updates to these guidelines regarding co-administration of antituberculous and antiretroviral drugs: 
http://www.cdc.gov/nchstp/tb/

Other possible combinations of antiretrovirals and rifamycins have also been recommended, however the published experience with such regimens is quite limited [MMWR 2000;49:185].
v) TUBERCULOUS IMMUNE RECONSTITUTION SYNDROME (MTB-IRS)

MTb-IRS is a paradoxical worsening of the signs and symptoms of tuberculosis, which occurs in 29-36% of MTb/HIV co-infected patients who receive antiretroviral therapy (ART) during the course of antituberculous therapy (Lancet Infect Dis 2005;5:361). Manifestations often include fevers, worsening pulmonary infiltrates, or lymphadenopathy, at a median of 4 weeks after starting ART. The diagnosis of MTb-IRS is one of exclusion and depends upon ruling out other opportunistic infections, multidrug resistant MTb (MDR-TB), drug reactions, etc. As for other immune reconstitution syndromes, the diagnosis requires evidence of a favourable virologic (HIV RNA reduction of ≥ 1 log_{10}) and/or immunologic (CD4 increase) response to the ART regimen. Anecdotal reports suggest a possible benefit of anti-inflammatory medications [e.g. corticosteroids].

Tuberculosis is reportable. Consultation and assistance is available from:

The BC Centre for Excellence in HIV/AIDS.................................................. 1-800-665-7677
TB Control, Ministry of Health, BCCDC..................................................... [604] 660-6108
New Westminster Chest Clinic................................................................. [604] 660-8829
Victoria and Island Chest Clinic............................................................. [250] 387-6295
8. PNEUMONIA [Community-acquired, CAP]

i) ETIOLOGY

Bacteria. The most important bacterial organisms include *Streptococcus pneumoniae* and *Haemophilus influenzae*. Among patients with advanced HIV disease, *Staphylococcus aureus* and gram-negative bacilli (including *Pseudomonas aeruginosa*) may also be responsible. Atypical bacterial pathogens (e.g. *Mycoplasma*) are seldom encountered [NEJM 1995;333:845. J Infect Dis 2001;184:268].

Other organisms. Tuberculosis occurs at any stage of HIV infection; however CD4 lymphopenia is typically associated with pneumonia due to *Pneumocystis jiroveci* (formerly PCP), atypical mycobacteria, *Cryptococcus, Histoplasma*, and *Aspergillus* species.

ii) DIAGNOSIS

Investigations for all patients should include: chest X-ray, blood cultures, sputum Gram’s stain and culture, CBC and differential count prior to starting antibiotic treatment [CID 2005;40:S131]. A normal LDH argues against a diagnosis of *Pneumocystis jiroveci* pneumonia (PJP) but does not exclude it; an elevated LDH is non-specific. Expectorated sputum is inadequate for the diagnosis of PJP, which depends upon collection of bronchoalveolar lavage specimens when PJP is suspected. Most HIV-positive patients should also have respiratory tract specimens for acid-fast bacilli (AFB) smears and mycobacterial cultures, except for those with an acute onset of illness (e.g. symptoms for only a few days) and no additional TB risk factors (aside from being HIV-positive) such as a history of positive tuberculin skin test (TST), TB exposure, IDU, homelessness and having been exposed to a high TB prevalence area. Serum cryptococcal antigen should be ordered for unexplained CAP; however a negative result does not exclude pulmonary cryptococcosis. For occasional patients with a compatible clinical picture and endemic zone exposure history, urine (+/- serum) should be sent for *Histoplasma* antigen assay [MiraVista Diagnostics, Indianapolis, IN]. Thoracentesis should be performed if a pleural effusion is large enough to sample. Although in selected patients urinary antigen tests for pneumococccus or *Legionella* have been recommended [Clin Infect Dis 2007;44:S27], the former is not offered by BCCDC, and the turn-around time for the latter [sent to Toronto] is 2-3 weeks.
iii) RESPIRATORY ISOLATION

The limited number of negative-pressure respiratory isolation beds in many hospitals makes it difficult to comply [Arch Intern Med 1994;154:326] with the CDC (Atlanta, GA) guidelines which specify respiratory isolation for all HIV-positive patients with unexplained cough and fever pending the results of respiratory tract specimens for AFB smears [MMWR 2005;54[RR12];1-81]. As a result, if there are insufficient isolation beds, priority for isolation should be given to those most likely to have pulmonary TB including those with: cavitary lesions, a miliary pattern, or hilar/mediastinal lymphadenopathy on chest X-ray; lack of response to empiric therapy for "bacterial pneumonia"; positive TST (and no history of TB treatment or prophylaxis); or additional risk factors for TB (e.g. history of TB or TB exposure, IDU, homelessness, First Nations, or and having been exposed to a high TB prevalence area).

iv) TREATMENT

a) Hospital admission criteria. Clinical predictors can identify patients at low risk for pneumonia-related complications or mortality who may be managed as outpatients [Clin Infect Dis 2007;44:S27]. However, among HIV-positive patients there are often other factors which make hospitalization necessary, including: diagnostic uncertainty regarding opportunistic pathogens, vomiting, decompensation of co-existing illness, poor overall functional status, cognitive dysfunction, severe psychiatric illness, homelessness, IDU, or other social problems (Chest 2003;124:2148. Arch Intern Med 2000;160:98. Clin Infect Dis 2007;44:S27).

b) Usual organisms: Cefotaxime (1-2 gm IV q8-12 hr) or ceftriaxone (1-2 gm IV q24 hr) plus a macrolide [clarithromycin XL 1000 mg PO daily or azithromycin 500 mg PO/IV 1st dose, then 250-500 mg PO/IV daily]. For penicillin-allergic patients, a respiratory fluoroquinolone (e.g. moxifloxacin 400 mg PO/IV daily or levofloxacin 500-750 mg PO/IV) is recommended [Clin Infect Dis 2007;44:S27]. However, empiric fluoroquinolone therapy for CAP should be avoided in patients when the suspicion for tuberculosis is moderate to high, given the potential for reducing the yield of TB diagnostic testing, delay in TB diagnosis, and possible development of TB quinolone resistance related to TB monotherapy [Clin Infect Dis 2002;34:1607]. Cefuroxime is not recommended for hospitalized patients given the greater likelihood (e.g. versus cefotaxime) of failed therapy and mortality among patients with bacteremic pneumococcal pneumonia due to organisms with reduced susceptibility to penicillin [drug-resistant S. pneumoniae, DRSP] [Clin Infect Dis 2003;37:230]. Improved survival has been observed in severe pneumococcal pneumonia (e.g. bacteremia) with combination antibiotic therapy, such as a beta-lactam plus a macrolide [vs beta-lactam monotherapy] [Am J Respir Crit Care Med 2004;170:440].
c) **Gram-negative pneumonia.** For patients with risk factors for gram-negative bacterial pneumonia (CD4 < 100/µL, neutropenia, bronchiectasis, or previous history of *Pseudomonas* infection) consider broader empiric antibiotic coverage with an anti-pseudomonal beta-lactam (piperacillin-tazobactam, imipenem or meropenem) plus either ciprofloxacin or high dose levofloxacin (750 mg/day) [Clin Infect Dis 2005;40:S131]. Alternatives include: a) an anti-pseudomonal beta-lactam (as above) plus an aminoglycoside plus azithromycin; or b) an anti-pseudomonal beta-lactam (as above) plus an aminoglycoside plus a respiratory quinolone (moxifloxacin or levofloxacin) [Clin Infect Dis 2007;44:S27].

d) **Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) pneumonia.** This remains a very uncommon cause of CAP, and accounts for 2% of all CA-MRSA infections, most of which involve soft tissues [NEJM 2005;352:1436]. CA-MRSA pneumonia should be suspected in patients presenting with pneumonia preceded by influenza and also those with cavitary infiltrates but no risk factors for anaerobic aspiration pneumonia. Other risk factors for *S. aureus* pneumonia include IDU, end-stage renal disease, and prior antibiotic therapy (particularly fluoroquinolones). A diagnosis of CA-MRSA pneumonia can usually be made with sputum and blood cultures, emphasizing the importance of getting an immediate sputum Gram’s stain result in suspected cases. For empiric therapy, the addition of linezolid 600 mg IV (step down to PO) q12 hr or vancomycin 20 mg/kg IV loading dose, the 15 mg/kg q 12 hr is recommended [Clin Infect Dis 2007;44:S27]. There is some evidence to suggest that linezolid may be superior to vancomycin for this indication [Chest 2003;124:1789]. Empiric antibiotic coverage for MRSA should be discontinued in patients whose blood and respiratory tract cultures are negative for the organism.
9. SYphilis

i)诊断和筛查

近期的梅毒流行主要发生在城市地区（Sex Transm Dis 2000;27:53），约50%的病例是同性恋男性，其中许多人同时也是HIV阳性。所有新诊断的HIV病例都应筛查梅毒（包括血清学检查）。同样，新诊断的梅毒病例也应检测HIV感染。在BC省筛查梅毒的血清学试验是快速反应素（RPR），这是一种非特异性试验。如果RPR呈阳性，则还需进行特异性梅毒抗体试验（如Treponema pallidum颗粒凝集试验，TPPA）以确认诊断。RPR为阳性结果时，则应进行特定的梅毒抗体试验。梅毒血清学试验的临床发现（如肉芽肿、一般化疹或神经症状），以及脊髓液VDRL和细胞计数，均用于确立梅毒的诊断及其阶段。HIV感染的患者，特别是同性恋者（如MMS和不采取安全措施）应定期进行梅毒筛查，包括RPR，每6个月一次。RPR对1期、2期和3期梅毒的敏感度分别为86%、100%和70%，各占Lancet ID 2004;4:456。

诊断神经梅毒

在HIV阳性患者中，没有单一试验同时敏感和特异性，推荐咨询。实验室诊断神经梅毒是通过脊液VDRL阳性（血样未被明显污染）进行的，而这种试验在没有广泛利用（可能在要求时获得）时是不敏感的。虽然特异性很高，但是VDRL在大约50%的病例中呈阴性。相反，CSF FTA-ABS（荧光Treponema抗体吸收试验）在排除神经梅毒时表现出高敏感性（但低特异性），这样，如果CSF FTA-ABS试验结果为阴性则可排除神经梅毒。无症状或有症状的HIV感染患者，如有不解释的CSF细胞数> 5淋巴细胞/µL或CSF蛋白升高，则应被诊断为神经梅毒。然而，HIV感染本身可引起CSF细胞数和蛋白升高的症状，这使得神经梅毒的诊断更为困难。高CSF细胞数（20白细胞/µL）或CSF VDRL阳性可被用来诊断神经梅毒在HIV感染患者中的临床试验（J Infect Dis 2004;189:369）中，但可能在某些情况下与诊断不足有关。
ii) LUMBAR PUNCTURE INDICATIONS

Lumbar puncture should be considered in all HIV-positive patients with positive syphilis serology, and is recommended in any of the following situations (J Infect Dis 2004;189:369. MMWR 2006;55[RR-11]:22):

a) 1\textsuperscript{st} or 2\textsuperscript{nd} syphilis with RPR > 1:32, or
b) late latent syphilis (duration ≥ 1 yr, or unknown), particularly with RPR ≥ 1:32, or
c) tertiary syphilis (e.g. aortitis, gummas), or
d) neurologic signs or symptoms, or
e) eye disease (e.g. uveitis) or auditory symptoms, or
f) CD4 < 350, or
g) treatment failure

iii) TREATMENT (MMWR 2006;55[RR-11]:22 and Health Canada STD Treatment Guidelines 2005)

a) Primary, secondary, and early (< 1 yr) latent syphilis. Benzathine penicillin G [Bicillin] 2.4 million units (1.2 m.u. in each buttock) IM once. **Penicillin allergy** (consider allergy consult for all patients, including skin testing +/- desensitization): doxycycline 100 mg PO BID x 14 days

b) Tertiary and late (> 1yr) latent syphilis. Benzathine penicillin G (Bicillin) 2.4 million units (1.2 m.u. in each buttock) IM weekly x 3 doses. **Penicillin allergy** (consider allergy consult for all patients, including skin testing +/- desensitization): ceftriaxone a possible option

c) Neurosyphilis. Aqueous crystalline penicillin G 3-4 million units IV q4h x 10-14 days (consider also giving benzathine penicillin G 2.4 million units [1.2 m.u. in each buttock] IM once on the last day of IV penicillin in order to provide a duration of penicillin comparable to the tertiary syphilis regimen). An alternative regimen is procaine penicillin G 2.4 m.u. IM daily + probenecid 500 mg PO QID, both for 10-14 days. **Penicillin allergy** (consider allergy consult for all patients, including skin testing +/- desensitization): ceftriaxone 2 gm IM/IV daily for 10-14 days.
iv) POST TREATMENT MONITORING (MMWR 2006;55[RR-11]:22)

a) Primary, secondary, and early latent syphilis. RPR every 3 months at 3, 6, 9, 12, and 24 months after treatment. Expect a ≥ 4 fold reduction in titer at 6-12 months with successful therapy.

b) Late latent syphilis. RPR at 6-month intervals at 6, 12, 18, and 24 months after treatment. Expect a ≥ 4 fold reduction in titer at 12-24 months with successful therapy.

c) Neurosyphilis. RPR every 3-6 months x 2 years. Repeat spinal fluid (CSF) testing every 6 months x 2 years. Expect CSF white blood cell count to have fallen at 6 months, and to have normalized by 2 years post treatment.
10. SKIN AND SOFT TISSUE INFECTIONS (SSTIs)

i) CELLULITIS
   a) No associated abscess, wound, or penetrating trauma
   b) Associated abscess, wound, or penetrating trauma [e.g. IDU]

ii) ERADICATION OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS [MRSA] COLONIZATION

iii) OPPORTUNISTIC INFECTIONS

iv) NECROTIZING FASCITIIS

i) CELLULITIS

a) No associated abscess, wound, or penetrating trauma. These infections are most often caused by β-hemolytic streptococci, usually group A, but also groups B, C, and G. Staphylococcus aureus is infrequently the cause (Clin Infect Dis 2005;41:1373. NEJM 2004;350-904).

Empiric antibiotic therapy should be directed against β-hemolytic streptococci:

- **mild infection** may be managed with cephalexin 500 mg PO QID x 5-10 days. If penicillin allergy: levofloxacin 500 mg PO daily, or clindamycin 300-450 mg PO TID, or erythromycin 250-500 mg PO QID. Group A β-hemolytic streptococci resistance to clindamycin and erythromycin was observed in 23% of isolates in 2006 at St. Paul’s Hospital, Vancouver.

- **moderate to severe infection** should be treated with cefazolin 1-2 gm IV q8h or cloxacillin 1-2 gm IV q4h. If penicillin allergy: vancomycin 15 mg/kg IV q12h or clindamycin 600 mg IV q8h.

b) Associated abscess, wound, or penetrating trauma (including injection drug use). These infections are often caused by Staphylococcus aureus, although others include anaerobes, β-hemolytic streptococci, and in some patients gram-negative rods [e.g. diabetics]. In some hospitals in Vancouver and the Lower Mainland, up to 50% or more of the S. aureus isolates are methicillin–resistant (MRSA).

Empiric antibiotic options should be directed against MRSA plus/minus β-hemolytic streptococci, plus/minus other organisms:

- **mild infections** may be treated with warm compresses and incision and drainage of abscesses. If antibiotic therapy is considered necessary, then the options include: trimethoprim-sulfamethoxazole (TMP-SMX) 1-2 DS tablets BID plus/minus cephalexin 500 mg PO QID x 5-10 days. TMP-SMX is not an effective drug for group A β-hemolytic streptococcal infection; therefore, if there is concern regarding β-hemolytic streptococci, then cephalexin should be added.

For documented MRSA infection, TMP-SMX or doxycycline may be used alone or in combination with either fuscidic acid 500 mg PO TID or rifampin 300 mg
PO BID, depending upon susceptibility results. Community-acquired MRSA (CA-MRSA) is usually susceptible to TMP-SMX, doxycycline, rifampin, and fusidic acid. Neither fusidic acid nor rifampin should be used as monotherapy for S. aureus, since the development of resistance is predictable. Rifampin is associated with numerous drug interactions.

- **moderate to severe infections** should be treated with incision and drainage of abscesses as needed plus vancomycin 15 mg/kg IV q12h or linezolid 600 mg PO/IV q12h. If susceptible, then clindamycin 600 mg IV q8h is another option.

**ii) ERADICATION OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) COLONIZATION.**

Patients with recurrent MRSA infections may be offered the following decolonization regimen [Clin Infect Dis 2007;44:178] provided that the MRSA is susceptible [Can J Infect Dis Med Microbiol 2006;17[suppl C]:4C-24C]:

- doxycycline 100 mg PO BID x 7 days, plus
- rifampin 300 mg PO BID x 7 days, plus
- mupirocin 2% ointment applied to the anterior nares TID with a cotton-tipped applicator, plus
- chlorhexidine gluconate 2% body wash daily x 7 days

Rifampin is associated with numerous drug interactions.

**iii) OPPORTUNISTIC INFECTIONS IN ADVANCED HIV INFECTION.**

Any SSTI that is not responding to empiric therapy or has atypical features should be considered for skin biopsy including special stains and cultures for bacteria, mycobacteria, viruses, and fungi.

- **Viruses.** Among patients with low CD4 counts, *Herpes simplex* often presents with persisting, spreading shallow ulcers, particularly on the face and anogenital areas. The diagnosis is established with viral culture. Varicella zoster virus (shingles or chickenpox) often can be reliably diagnosed clinically, but confirmation by lesion Tzanck smear, antigen detection, or culture may be needed.

- **Fungi.** Disseminated infection due to *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Aspergillus species*, and *Penicillium marneffei* may include cutaneous lesions.

- **Bacteria.** Unusual bacterial SSTIs include *Nocardia* species, mycobacteria, *Bartonella henselae* (bacillary angiomatosis), *Pseudomonas aeruginosa*, and *Helicobacter cinaedi*. 
iv) NECROTIZING FASCIITIS

- Type 1 necrotizing fasciitis is a polymicrobial infection, which usually occurs in the setting of diabetes, recent surgery or trauma. Clinical features include toxicity, pus, and possibly gas formation in tissues. **Management** includes broad spectrum antibiotic coverage, surgical debridement, and supportive care.

- Type 2 necrotizing fasciitis is due to group A β-hemolytic streptococci and risk factors include HIV infection (relative risk, RR 9.4), heart disease (RR 8.4), cancer (RR 6.9), and diabetes (RR 3.7) (NEJM 1996;335:547). Approximately 50% of cases are associated with streptococcal toxic shock syndrome, but pus and gas formation in tissues is typically absent. The diagnosis of necrotizing fasciitis should be considered if any of the following are present: a) SSTI associated with severe pain or toxicity; b) extensive induration of subcutaneous tissue extending beyond the area of apparent skin involvement; c) bullous lesions, particularly if hemorrhagic; d) skin necrosis or ecchymoses; e) compartment syndrome; f) hemodynamic instability or evidence of multi-organ failure (associated toxic shock); g) elevated CK; or h) bacteremia due to group A β-hemolytic streptococcus. **Management** includes: empiric antibiotic therapy [e.g. IV clindamycin, penicillin, +/- imipenem, +/- vancomycin] until the etiology is determined; plus urgent surgical debridement. Intravenous immune globulin (IVIG) is recommended for patients who also have toxic shock syndrome (2 grams/kg, then reassess in 24 hr and possibly give a second dose)(Clin Infect Dis 1999;28:800).
11. CYTOMEGALOVIRUS DISEASE

i) PROPHYLAXIS

Two comparative clinical trials of oral ganciclovir as prophylaxis in patients with CD4 counts \(< 50/\text{mm}^3\) have yielded conflicting results regarding efficacy (NEJM 1996;334:1491. AIDS 1998;12:269). Prevention strategies in patients with CD4 counts \(< 50/\text{mm}^3\) (oral ganciclovir prophylaxis or pre-emptive therapy with q3monthly monitoring of blood samples for CMV DNA by PCR and initiating ganciclovir for patients with positive tests) do not appear to be cost effective (AIDS 1997;11:883) and have not been widely adopted.

ii) THERAPY

Indications:

a) **CMV Retinitis.** Indicated for all patients with CMV retinitis. Cases should be confirmed by an experienced ophthalmologist, although treatment should not be delayed in suspected cases.

1. Induction therapy options:
   - Most patients can be successfully induced with oral valganciclovir, which is easily administered and well tolerated (Clin Infect Dis 2005;40:S131). However, patients with sight-threatening zone 1 disease (involving the posterior pole in the vicinity of the macula or optic disc, i.e. \(< 1500\) microns from the fovea) but useful vision still preserved should be strongly considered for initial local therapy (intraocular injections or the intraocular ganciclovir implant plus oral valganciclovir) or intravenous ganciclovir. Subsequent intraocular injections are not required for those simultaneously started on oral valganciclovir. Intravenous ganciclovir can be stepped down to oral valganciclovir after 72 hours.
   - Oral: valganciclovir
   - Intravenous: ganciclovir (alternatives: foscarnet; cidofovir)

Cytomegalovirus (CMV) disease should be managed by a qualified specialist in conjunction with an experienced ophthalmologist.
• Intraocular (+/- systemic):
  
a) ganciclovir implant +/- oral valganciclovir

  b) injections: ganciclovir, or foscarnet, +/- oral valganciclovir

Induction Therapy Considerations:

**ORAL**

• **Valganciclovir** is a ganciclovir prodrug with improved oral bioavailability compared to oral ganciclovir. It has been shown to have similar tolerance and efficacy to IV ganciclovir in a comparative trial of induction therapy of HIV-related CMV retinitis [NEJM 2002;346:1119]. However, this study excluded patients with immediately sight-threatening CMV retinitis (lesions < 1500 microns from the fovea centralis), where it may be preferable to give induction therapy with ganciclovir either locally (e.g. intravitreal injections) or intravenously, which would be expected to rapidly achieve therapeutic intraocular drug levels.

**INTRAOCULAR GANCICLOVIR IMPLANT**

This form of treatment (one or both eyes) should be considered both in patients with a new diagnosis and those with pre-existing disease, but is not appropriate for those with a life expectancy of only a few months. This is the most effective form of treatment but involves major ocular surgery, and may be associated with complications including endophthalmitis and retinal detachment. Also, few ophthalmologists have experience with the procedure. Vision transiently worsens during the first few weeks after the implant is inserted [NEJM 1997;337:83]. A disadvantage of local treatment is the greater risk of developing disease which is extraocular or involving the contralateral eye, unless it is combined with systemic therapy (e.g. oral valganciclovir) [NEJM 1999;340:1063]. Patients with sight-
threatening zone 1 disease (involving the posterior pole in the vicinity of the macula or optic disc, i.e. < 1500 microns from the fovea) but useful vision still preserved should be strongly considered for the intraocular ganciclovir implant.

2. Re-induction therapy:

Early relapses (< 3 months). Most relapses of retinitis during the first few months of therapy are related to inadequate ocular penetration of systemically administered drugs, rather than drug resistance (J Infect Dis 1993;168:1506). Changing to a different antiviral drug at the first relapse has not been associated with improved disease control, unless dictated by drug toxicity or particular suspicion of drug resistance. Placement of a ganciclovir implant may be preferable in this situation. Alternatively, reinduction may be accomplished using the same drug being used for maintenance therapy.

Late relapses (after 3 months). Subsequent relapses are more likely to be associated with drug resistance. Resistant rates for CMV are usually < 10% during the first 3 months of therapy, but increase to 25-30% at 9 months (CID 2005;40:S131). However, in a recent observational study, CMV resistance rates at 2 years for patients enrolled in the pre- and post-HAART era [after 1996] were 28% and 9%, respectively (Clin Infect Dis 2007;44:1001). Low-and high-level ganciclovir resistance is related to mutations in the CMV UL97 (phosphotransferase) gene and both the UL97 and UL54 (DNA polymerase) genes, respectively (J Infect Dis 1997;176:69). High-level ganciclovir resistance is often associated with cross-resistance to cidofovir, and sometimes also to foscanet (J Infect Dis 2000;182:1765). Resistance testing for CMV is not widely available, however using CMV DNA PCR and sequencing for the UL97 mutation, it may be possible to guide treatment decisions in patients with multiple relapses [CID 2005;40:S131]. The following are reinduction options for late relapses (> 3 months):

a) switching from oral valganciclovir to IV foscarnet, or
b) switching to cidofovir, or
c) intravitreal ganciclovir implant + oral valganciclovir,
d) switching to, or adding intraocular injections [ganciclovir, or foscanet]
e) combined IV ganciclovir plus foscanet

Considerations regarding drug selection: Treatment options should be considered in regard to potential adverse effects, efficacy, drug interactions, likelihood of resistance, and patient preference.
3. Maintenance therapy:
Optimal therapy for CMV retinitis is immune reconstitution with HAART; but until that occurs (see below) specific anti-CMV therapy must be maintained (Eur J Clin Microbiol Infect Dis 2000;19:571).

Approximate median times to progression with the different treatments are as follows: intraocular ganciclovir implant 196-226 days; IV ganciclovir 49-70 days; foscarnet 53-93 days; oral ganciclovir 29-56 days; and cidofovir 64-120 days. Prior to valganciclovir, the most effective anti-CMV maintenance regimen was the combination of intraocular ganciclovir implant plus oral ganciclovir 4.5 gm/day, which reduced the incidence of contralateral retinitis and extraocular CMV disease (NEJM 1999;340:1063). Oral ganciclovir is no longer available, having been replaced by valganciclovir. However, among patients receiving oral valganciclovir plus HAART, the time at which 25% of patients had progressed was 456 days (ICAAC 2000, abstr. 776).

MAINTENANCE THERAPY OPTIONS:
• Oral: valganciclovir
• Intravenous: ganciclovir (alternatives: foscarnet; cidofovir)
• Intraocular (+ systemic):
  a) ganciclovir implant (one or both eyes) + oral valganciclovir, or
  b) intravitreal injections: ganciclovir, or foscarnet, + oral valganciclovir

Discontinuing maintenance therapy may be considered for selected patients who have antiretroviral therapy induced sustained increases in CD4 count to > 100-150 cells/mm³ for at least 6 months. The decision to recommend discontinuation should be individualized and take into account various factors including: durability of suppression of HIV RNA; adherence to HAART; the anatomic location of the healed retinal lesions (posterior pole [i.e. zone 1] lesions are of greater concern than peripheral lesions); vision in the contralateral eye; and the likelihood of regular ophthalmologic follow-up (Clin Infect Dis 2004;40:S131).

4. Antiviral drug contraindications and dosages:
Contraindications (relative or absolute):

  ganciclovir: neutrophils < 0.5 (despite G-CSF), severe thrombocytopenia (< 20)

Precaution: zidovudine (AZT)- containing antiretroviral regimens in addition to ganciclovir induction therapy frequently result in additive bone marrow toxicity
valganciclovir: severe diarrhea may result in inadequate absorption
foscarnet: renal impairment, concomitant nephrotoxic drugs

Precaution: IV infusion of 500-1000 cc normal saline just before or with the foscarnet dose may reduce the risk of nephrotoxicity
cidofovir: renal impairment, neutrophils < 0.5, concomitant nephrotoxic drugs, or if probenecid contraindicated

Precaution: In order to minimize nephrotoxicity, probenecid must be given in a dosage of 2 g three hours before the cidofovir infusion, followed by 1 g of probenecid 2 hours and 8 hours after the infusion. One litre of saline should be infused during the 1-2 hour period immediately before the cidofovir infusion, which is then given in 100 mL normal saline. Patients who are able to tolerate an additional fluid load should be given a second litre of normal saline either during or immediately after the cidofovir infusion and run over 1-3 hours. Cidofovir is contraindicated in patients with renal impairment (serum creatinine > 133 µmol/L). The cidofovir dosage for each infusion should be reduced to 3 mg/kg if there is a significant increase in serum creatinine (27-43 mmol/L above baseline). Cidofovir should be discontinued if the serum creatinine rises by ≥ 44 mmol/L above baseline or if significant proteinuria (≥ 3+, or persistent 2+ proteinuria [1.0 g/L]) develops. Cidofovir also must be discontinued if the patient is unable to take probenecid (hypersensitivity, intolerance) or if there is a significant decrease in intraocular pressure (ocular hypotony).

<table>
<thead>
<tr>
<th>Drug Dosages:</th>
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<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>Valganciclovir</td>
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<tr>
<td>Ganciclovir</td>
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<td>Ganciclovir (high dose)</td>
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<td>Ganciclovir implant</td>
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<td>Ganciclovir intraocular</td>
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<td>Foscarnet</td>
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<tr>
<td>Foscarnet intraocular</td>
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<tr>
<td>Cidofovir</td>
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b) CMV esophagitis or colitis (biopsy proven):

INDUCTION TREATMENT:

- IV ganciclovir or foscarnet, as recommended for retinitis; however, the induction therapy duration is for 3-4 weeks (rather than 2-3 weeks).
- Valganciclovir as recommended for retinitis is an option if the patient can swallow and diarrhea is not severe enough to impair absorption.

MAINTENANCE THERAPY:

not required unless there are recurrences (see CMV retinitis maintenance therapy options).

c) CMV pneumonitis

Evidence of CMV in respiratory tract specimens of HIV-infected patients has a low predictive value for the presence of CMV pneumonitis. Antiviral therapy is recommended for patients with histologic evidence of CMV pneumonia in the absence of other respiratory pathogens or those not responding to the treatment of other co-pathogens [Clin Infect Dis 2005;40:S131]. Induction and maintenance treatment should be given as for CMV retinitis until further data are available. Maintenance therapy may not be required.

d) CMV encephalitis or polyradiculopathy.

The response to therapy with either ganciclovir or foscarnet is often suboptimal. Combined IV ganciclovir plus foscarnet is recommended [AIDS 2000;14:517].

iii) CMV IMMUNE RECONSTITUTION SYNDROME (CMV-IRS)

Most reports of CMV-IRS have involved ocular CMV infection and have been named immune recovery vitritis (CMV-IRV) or uveitis. CMV-IRV has been defined as the presence of at least 1+ vitritis on examination plus ocular symptoms (floaters or reduced vision of ≥ 1 line on the eye chart) in patients on antiretroviral therapy (ART) who have had previous CMV retinitis [J Infect Dis 1999;179:697]. Other ocular complications of CMV-IRV include macular or optic disc edema (papillitis), epiretinal membrane formation, neovascularization and progressive visual loss. In most cases the CMV retinitis is inactive. The incidence of CMV-IRV has been reported in up to 63% of patients with a history of prior CMV retinitis and develops at a median of 43 weeks after initiation of ART [J Infect Dis 1999;179:697]. There have been no controlled trials of therapy for CMV-IRV, and the efficacy of suggested interventions remains unclear. However patients are often treated with corticosteroids or anti-CMV antivirals. [Br J Ophthalmol 1999;83:540. Am J Ophthalmol 2004;137:636].
12. HERPES SIMPLEX

i) PROPHYLAXIS

Indicated only for patients with documented frequent or severe recurrences. Options include (CID 2006;43:347):

- acyclovir 400-800 mg PO BID or TID, or
- famciclovir 500 mg PO BID, or
- valacyclovir 500 mg PO BID

ii) TREATMENT:

a) Mild to moderate mucocutaneous infection (e.g. orolabial or genital)
   Treat until lesions have healed, usually for 7-14 days. Options include:
   - acyclovir 400 mg PO 3-5 times a day; or
   - famciclovir 500 mg PO BID, or
   - valacyclovir 1000 mg PO BID

b) Severe mucocutaneous infection
   Acyclovir 5 mg/kg IV q8h [dosage adjustment needed for renal impairment] (CID 2005;40:S131]. Intravenous acyclovir infusions should be given over at least 1 hour to reduce the risk of nephrotoxicity. Monitor renal function every 1-2 days and minimize nephrotoxicity of IV acyclovir by avoiding intravascular volume depletion. As lesions improve, step down to oral therapy as for mild to moderate mucocutaneous infection (see above).

c) Visceral (e.g. HSV encephalitis) or disseminated cutaneous infection
   Acyclovir 10 mg/kg IV q8h [dosage adjustment needed for renal impairment]. Intravenous acyclovir infusions should be given over at least 1 hour to reduce the risk of nephrotoxicity. Monitor renal function every 1-2 days and minimize nephrotoxicity of IV acyclovir by avoiding intravascular volume depletion.
d) **Acyclovir-resistant infection.**

This should be suspected in patients with culture-proven HSV infection who do not respond to therapy with IV or high dose oral acyclovir (400-800 mg PO 5x/day). Susceptibility (or genotypic resistance) testing is not readily available, so that a diagnosis of acyclovir-resistant infection is made on clinical grounds. Treatment options should be continued until lesions have healed (possibly weeks or months for extensive disease) and include:

- **foscarnet** 40 - 60 mg/kg IV q8h or 60-90 mg/kg q12h,
  [see CMV infections for adverse effects, administration and monitoring] [NEJM 1991;325:551] or

- **cidofovir** 5 mg/kg IV once weekly [see CMV infections for adverse effects, administration and monitoring] [J Infect Dis 1997;176:892],

13. VARICELLA ZOSTER VIRUS (VZV)

i) PROPHYLAXIS

a) Varicella zoster immune globulin (VZIG) is indicated within 96 hours of exposure for individuals who do not have a history of Varicella or herpes zoster and who also do not have an antibody titer (may be available within 1 day in some laboratories) to VZV. If VZIG is unavailable, then prophylactic acyclovir (famciclovir or valacyclovir) could be considered, although the efficacy of these drugs in this setting is unknown.

b) VZV vaccine. There is insufficient experience with this vaccine in HIV-infected patients to recommend its use at the present time [Ann Intern Med 2002;137:435].

c) Antiviral drugs. No antiviral drug has been demonstrated to prevent recurrent shingles in HIV-positive patients; and long-term suppressive therapy (primary or secondary prophylaxis) has not been recommended for VZV infection [Ann Intern Med 2002;137:435].


a) Primary Varicella infection (Chickenpox).
   Acyclovir 10 mg/kg IV q8h x 7-10 day. To reduce the risk of nephrotoxicity, all IV acyclovir infusions should be given over at least 1 hour, and intravascular volume depletion should be avoided. Renal function should be monitored every 1-2 days. Step down to oral therapy (valacyclovir 1 gram or famciclovir 500 mg TID) when afebrile, provided there is no evidence of visceral infection. For VZV infection, higher and more reliable levels of antiviral activity are achieved in blood with famciclovir or valacyclovir rather than acyclovir.

b) Dermatomal herpes zoster
   Mild to moderate disease should be treated (preferably within 72 hr of rash onset) with famciclovir 500 mg PO TID [Ann Intern Med 1995;123:89], or valacyclovir 1 gm PO TID for 7-10 days [AAC 1995;39:1546]. For VZV infection, higher and more reliable levels of antiviral activity are achieved in blood with famciclovir or valacyclovir rather than acyclovir (800 mg PO 5x/day). Patients presenting > 72 hr after rash onset should also be considered for antiviral therapy, particularly if any...
of the following are present: ongoing new vesicle formation; ocular or neurologic complications; or risk factors for post herpetic neuralgia (older age or severe pain) [Clin Infect Dis 2007;44:S1-26].

c) Multi-dermatomal, or ophthalmic herpes zoster, or progressive outer retinal necrosis.
Acyclovir 10 mg/kg IV q8h x 7-14 days should be started preferably within 72 hr of rash onset, and continued until lesions have resolved. To reduce the risk of nephrotoxicity, all IV acyclovir infusions should be given over at least 1 hour, and intravascular volume depletion should be avoided. Renal function should be monitored every 1-2 days. Urgent ophthalmology consultation is required for all patients with ocular involvement.

d) Relapsing disease and failed therapy
• Herpes zoster frequently occurs early in the course of HIV infection and is often a marker of declining immunity. Recurrent episodes may occur in the context of progressive HIV disease, but also may be seen as an immune reconstitution disease in 7-8% of patients who have recently started antiretroviral therapy (Am J Med 2001;110:605).

• Patients with persistent hyperkeratotic lesions following zoster may have acyclovir-resistant strains of Varicella zoster virus and should have a culture collected to document persistent infection despite antiviral therapy. However, susceptibility testing and genotypic resistance testing are not widely available. A trial of IV acyclovir is often warranted; however non-responders should receive foscarnet 40 mg/kg IV every 8 hours or 60-90 mg IV every 12 hours for at least 10 days [Ann Intern Med 1991:115:19] (see CMV infection regarding drug toxicity and monitoring).

iii) POST HERPETIC NEURALGIA AND ADJUNCTIVE THERAPY.
Famiciclovir and valacyclovir are superior to acyclovir for reducing the likelihood of prolonged pain [Clin Infect Dis 2007;44:S1-26].

a) Analgesics
• Mild-moderate pain: acetaminophen +/- codeine or NSAIDs q6h to obtain constant analgesia rather than on a PRN (as-needed) basis.

• Moderate-severe pain: use a potent opioid analgesic (e.g. oxycodone 5mg QID +/- acetaminophen, or morphine). When the effective dose has been determined, then switch to a long acting opioid. To avoid opiate-induced constipation, use laxative and stool softener therapy preemptively.
b) **Gabapentin.**  
Consider for patients with moderate-severe pain not well controlled with opioid analgesics. Due to possible sedation, the initial dosing should be 300 mg at bedtime, and subsequent dosage increases to 300 mg BID (day 2), then 300mg TID (day 3). The maximum daily dose is 3600 mg.

c) **Tricyclic antidepressants** (particularly nortriptyline).  
Consider for patients with moderate-severe pain not well controlled with opioid analgesics. Due to possible sedation, the initial dosing for nortriptyline should be 25 mg at bedtime (less for frail or elderly patients). The dose can be adjusted by 25 mg increments every 2-3 days as tolerated until pain is controlled or a maximum daily dose of 150 mg is reached.

d) **Corticosteroids.**  
Although prednisone may be indicated for selected HIV-negative patients, corticosteroids have not been evaluated in HIV-positive patients and are not recommended [Clin Infect Dis 2005;40:S131. Clin Infect Dis 2007;44:S1].
14. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) (POLYOMAVIRUS JC, OR JC VIRUS)

i) DIAGNOSIS

A diagnosis of PML requires all three of the following criteria:

a) Symptoms and physical signs compatible with PML

PLUS

b) MRI findings compatible with PML. Typically, multifocal white matter demyelination lesions are hypodense on CT (reduced signal on MR), non-enhancing with contrast, and not associated with edema or mass effect (Am J Neuroradiol 1999;20:1896). Atypical imaging findings including inflammatory lesions have been observed in HAART recipients with biopsy proven PML (Am J Med 1998;105:541) as an immune reconstitution syndrome.

PLUS

c) Either brain biopsy (gold standard; sensitivity 64-96%, specificity 100%; Neurology 1999;52:253) findings confirming PML or spinal fluid JCV PCR positive for JC virus. In the pre-HAART era, spinal fluid JCV PCR sensitivity was 72-92% and specificity 92-100% (AIDS 1997; 11:1); however, patients on HAART may present with a PML clinical picture but negative spinal fluid PCR (J Clin Microbiol 2005; 43:4175). JC virus levels in spinal fluid should be determined quantitatively, given the favourable prognostic value of low levels (e.g. 50-100 copies/ml) (Ann Neurol 1999;45:816).

ii) TREATMENT

HAART has been demonstrated to have a beneficial effect on the course of PML (AIDS 1998;12:2467. CID 2000;30:95), and should preferably include drugs which penetrate well into the CSF (e.g. abacavir, lopinavir-ritonavir). The 1-year survival in HIV-related PML with and without HAART has been 50 and 10%, respectively (J Neurovirol 2003;9 Suppl 1:47).

Specific antiviral therapy. No drug has been shown to be effective in clinical trials, despite some anecdotal reports of benefit. Previous studies have demonstrated lack of efficacy for interferon alpha-2b (J Neurovirol 2001;7:353), cytarabine (NEJM 1998;338:1345), cidofovir (AIDS 2002;16:1791. JAIDS 2004;37:1263), and the topoisomerase inhibitor topotecan (J Neurovirol 2003;9:411).
iii) PML IMMUNE RECONSTITUTION SYNDROME (PML-IRS)

Some patients may experience mild worsening of PML symptoms associated with initiation of HAART and not require any specific intervention. However, others with significant clinical deterioration associated with intracranial lesions showing brain swelling and mass effect should be considered for dexamethasone (8 mg QID for 2 weeks, then a gradual tapering dosage) and interruption of HAART, based upon anecdotal evidence of benefit in this situation (Neurology 2006;67:1692). Fatal cases of PML-IRS have been reported (Clin Infect Dis 2002;35:1250).