Common AIDS-associated opportunistic infections

ELC Ong MBBS MSC FRCP FRCPI DTMH, Consultant Physician and Honorary Senior Lecturer, *Department of Infection and Tropical Medicine, Newcastle General Hospital, Newcastle upon Tyne*

Clin Med 2008;8:539–43

HIV impairs the immune system, leaving the infected person susceptible to a variety of infections, called 'opportunistic' infections (OI). The effect of HIV on the immune system is monitored by measuring the CD4 (T-helper) lymphocyte count in the blood:

- *About 600–1,200 cells/μl*: normal, indicating that the immune system has not undergone sufficient damage to put the individual at risk for opportunistic illness. Such individuals are unlikely to require treatment or benefit from highly active antiretroviral therapy (HAART).
- *Below 350 cells/μl*: there is some impairment of immune function which should prompt consideration of HAART.
- *Below 200 cells/μl*: imminent risk of serious OIs or other complications of HIV disease. Prompt treatment is recommended.[1]

The development of secondary OIs in patients with HIV infection also results from interactions between specific organisms and host defences. AIDS-defining infections such as *Pneumocystis* pneumonia (caused by *P. jiroveci)* tend to occur later in the course of HIV infection when there is substantial depletion of the CD4 cells.[2] The late emergence of *P. carinii* pneumonia (PCP) relates to the relatively low pathogenicity of *P. carinii* compared with other organisms like *Mycobacterium* tuberculosis. The latter organism can cause disease earlier in the course of HIV infection. Figure 1 shows schematically the sequence of OIs in the natural history of HIV.

Pneumocystis pneumonia

PCP is the most common life-threatening infection in patients with AIDS in Europe and the USA. In the initial years of the epidemic it was responsible for up to 85% of all respiratory episodes.[3] The incidence of PCP as the first AIDS-defining condition still remains substantial, although it is progressively declining with the widespread use of prophylaxis and HAART.[4]

Although the causative agent of pneumocystosis was long considered a protozoan, studies of ribosomal RNA from the organism have shown greater homology with fungi. In 2001, *P. carinii* was officially reclassified as a fungus and was renamed *P. jiroveci*. Despite the name change, the disease is still referred to as PCP (*Pneumocystis* pneumonia). Such a reclassification has no immediate clinical importance, but it may suggest new therapeutic approaches.

P. jiroveci has both intracystic and extracystic forms. The cysts are oval or round, approximately 5–8 μm in diameter, and contain 4 to 8 intracystic organisms (sporozoites). The sporozoites are nucleated and measure approximately 1–2 μm in diameter. The extracystic form (trophozoite) measures 2–5 μm in diameter. It is pleomorphic and often has an eccentric nucleus.

The disease ranges in severity from a mild infection with a normal chest radiograph and an indolent course to respiratory failure requiring assisted ventilation where the mortality may exceed 90%.[5]

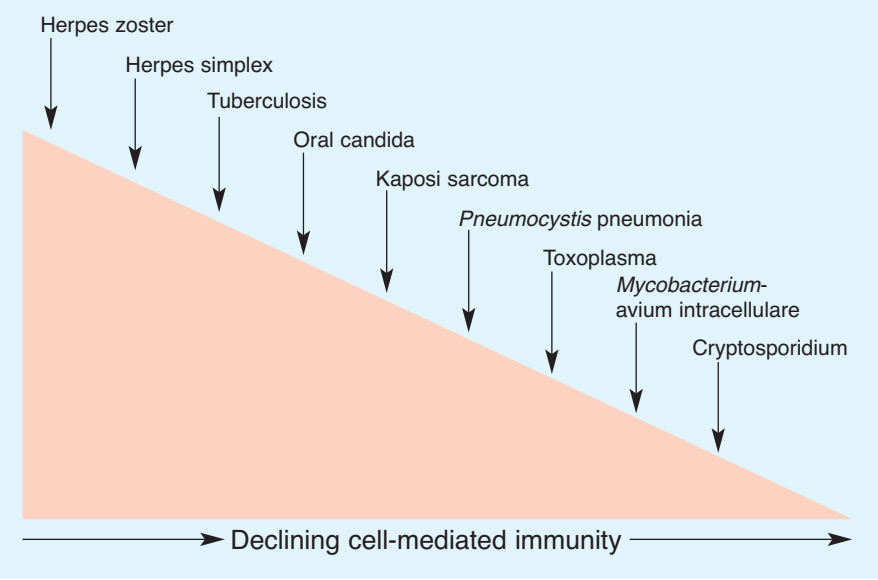

Fig 1. Sequence of opportunistic infections during natural history of HIV infection.

Key Points

- **CD4 (T-helper) lymphocyte count is the most important indicator of immunocompetence of a HIV-infected invididual**
- ***P. jiroveci* is the most common life-threatening infection in patients with AIDS**
- **Toxoplasmosis is an important cause of focal brain lesions**
- **Cryptococcosis is the cause of the most common life-threatening meningitis in AIDS**

KEY WORDS: CD4 count, cryptococcosis, pneumocystis, toxoplasmosis

PCP usually presents as a diffuse pulmonary infiltrate associated with fever, chest tightness, cough and breathlessness. A typical diffuse pulmonary infiltrate of PCP is shown in Fig 2.

Some patients may complain of wheeze.[6] It is important not to discount symptoms in patients even with a normal chest radiograph as 5–14% of patients subsequently found to have respiratory disease had a normal chest radiograph at presentation.[7] Severe cases of PCP frequently show extensive consolidation with air bronchograms and 5–10% show atypical features, including cystic changes, localised upper zone changes and miliary pattern, hilar and mediastinal lymphadenopathy and pleural effusion.

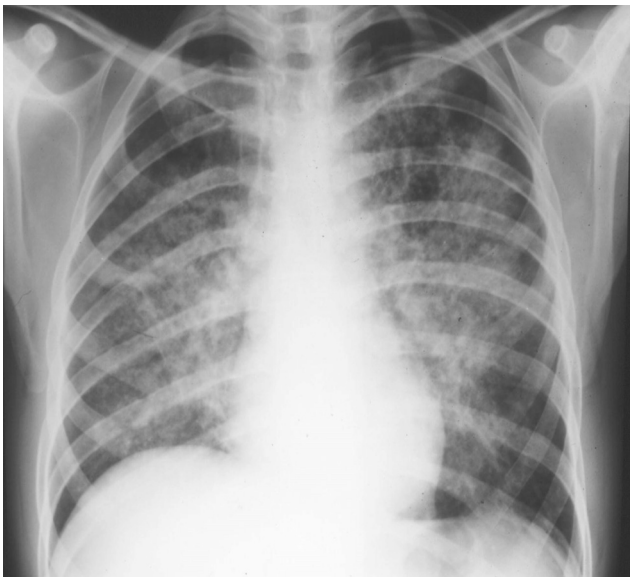

Fig 2. Chest X-ray showing typical diffuse pulmonary infiltrate of *Pneumocystis carinii* pneumonia.

Diagnosis

PCP is most readily diagnosed by induced sputum examination. The yield ranges from 70–95%, although the sensitivity is reduced by 20% if patients are on prophylaxis.[8] Almost all cases of PCP can be diagnosed by bronchoalveolar lavage; transbronchial and open lung biopsies are rarely necessary. Giemsa, toluidine blue O, methenamine silver, Gram's stain and immunofluorescent monoclonal antibody techniques are commonly used for diagnostic staining.

Treatment

High dose co-trimoxazole (trimethoprim-sulfamethoxazole (TMP-SMX)) given for 21 days is the treatment of choice for PCP. The standard dosage used in patients with advanced HIV disease was 20 mg/kg/day of TMP plus 100 mg/kg/day of SMX given either orally or intravenously (divided every 6 or 8 hours daily). Subsequent reports described similar efficacy and a lower frequency of adverse reactions with a dosage of 15 mg/kg/day of TMP and 75 mg/kg/day of SMX for 14–21 days. This has become the standard dosing regimen for acute PCP in adults.

Side effects are common and may occur in up to 50–80% of patients with HIV.[9] Hypersensitivity reactions, bone marrow suppression and hepatotoxicity are well recognised. Clindamycin with primaquine, parenteral pentamidine, trimetrexate and atovaquone are alternatives. Adjunctive therapy with corticosteroids has been shown to be of benefit if administered in the early stages of PCP for those with moderate to severe disease.[10]

HIV-infected patients with CD4 counts below 200 cells/μl or who have survived an episode of PCP should receive prophylaxis against PCP. In general, TMP-SMX (1 double-strength tablet daily or 3 times weekly) should be the first choice of prophylaxis for patients without a prior history of adverse reactions to that drug combination. Dapsone, dapsone-pyrimethamine and atovaquone are suitable alternatives for patients unable to take TMP-SMX for prophylaxis. Aerosolised pentamidine (300 mg every 4 weeks via the Respirgard II nebuliser or equivalent) is an alternative for those who do not tolerate the oral regimens.

Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan of worldwide distribution. Feline animals are the definitive hosts for the parasite and human infection occurs usually as a result of ingestion of ether food contaminated with cat faeces or undercooked meat from an infected animal.

Development of cell-mediated immunity after acute infection with *T. gondii* results in control but not eradication of the infection. The ensuing chronic or latent phase of infection is characterised by the persistence of the organism in tissues of the infected individual (primarily brain, skeletal muscle, and heart). Indeed, *T. gondii* is one of the most common causes of chronic infection with an intracellular organism in humans. A chronically infected individual who develops defects in cell-mediated immunity is at risk for reactivation of the infection. Toxoplasmosis in this setting manifests primarily as toxoplasmic encephalitis. This disease is an important cause of focal brain lesions in HIV-infected patients (Fig 3).[11]

Clinical features

Characteristically, TE has a subacute onset with focal neurological abnormalities, frequently accompanied by headache, altered mental status and fever. The most common focal neurological signs are motor weakness and speech disturbances. Patients can also present with seizures, cranial nerve abnormalities, visual field defects, sensory disturbances, cerebellar dysfunction, meningismus, movement disorders and neuropsychiatric manifestations. Toxoplasmosis rarely presents as a rapidly fatal form of diffuse encephalitis. Diffuse TE should be considered in patients with anti-*Toxoplasma*

gondii immunoglobulin G antibodies and CD4 T-cell counts below 100/μl, who present with unexplained neurological disease.

HIV-infected patients may develop extracerebral toxoplasmosis with or without concomitant encephalitis. Ocular and pulmonary disease are the most common presentations in patients with extracerebral toxoplasmosis. Patients with chorioretinitis present with blurred vision, scotoma, pain or photophobia. Ophthalmological examination reveals multifocal, bilateral lesions typically more confluent, thick and opaque than those caused by cytomegalovirus (CMV). Vitritis may be accompanied by anterior uveitis. *T. gondii* is a much less common cause of chorioretinitis in HIV-infected patients than CMV.

The clinical presentation of patients with pulmonary toxoplasmosis may be difficult to distinguish from PCP.[12] A highly lethal syndrome of disseminated toxoplasmosis comprising fever and sepsis-like syndrome with hypotension, disseminated intravascular coagulation, elevated lactic dehydrogenase and pulmonary infiltrates has been described in HIV-infected patients.

Diagnosis

T. gondii infection is detected by serological studies. Disease caused by the parasite (toxoplasmosis) can be diagnosed by demonstration of tachyzoites in tissue biopsies or cytological preparations of body fluids, isolation of *T. gondii* from body fluids or blood, or amplification of parasite DNA in body fluids or blood by polymerase chain reaction.

Treatment

Pyrimethamine (a dihydrofolate reductase inhibitor) is considered the cornerstone in the treatment of toxoplasmosis. In combination with sulfadiazine (a dihydrofolate synthase inhibitor) it is the standard regimen for treatment of TE. Patients receiving pyrimethamine should also be given folinic acid to prevent haematological adverse effects.

The combination of pyrimethamine and clindamycin is as effective as pyrimethamine and sulfadiazine during the acute phase of therapy,[13] although rash and diarrhoea are common adverse effects. A randomised, prospective study reported that TMP-SMX is as effective as pyrimethamine plus sulfadiazine for the treatment of TE.[14]

From limited data it appears that AIDS patients with extracerebral toxoplasmosis respond to pyrimethamine plus either sulfadiazine or clindamycin. The mortality rate in patients with pulmonary or disseminated toxoplasmosis may be higher than in those with TE alone. Patients with AIDS-associated toxoplasmosis should therefore be placed on a maintenance regimen on completion of the acute phase of treatment. Maintenance therapy typically consists of the same drugs used for primary therapy but at lower dosages.

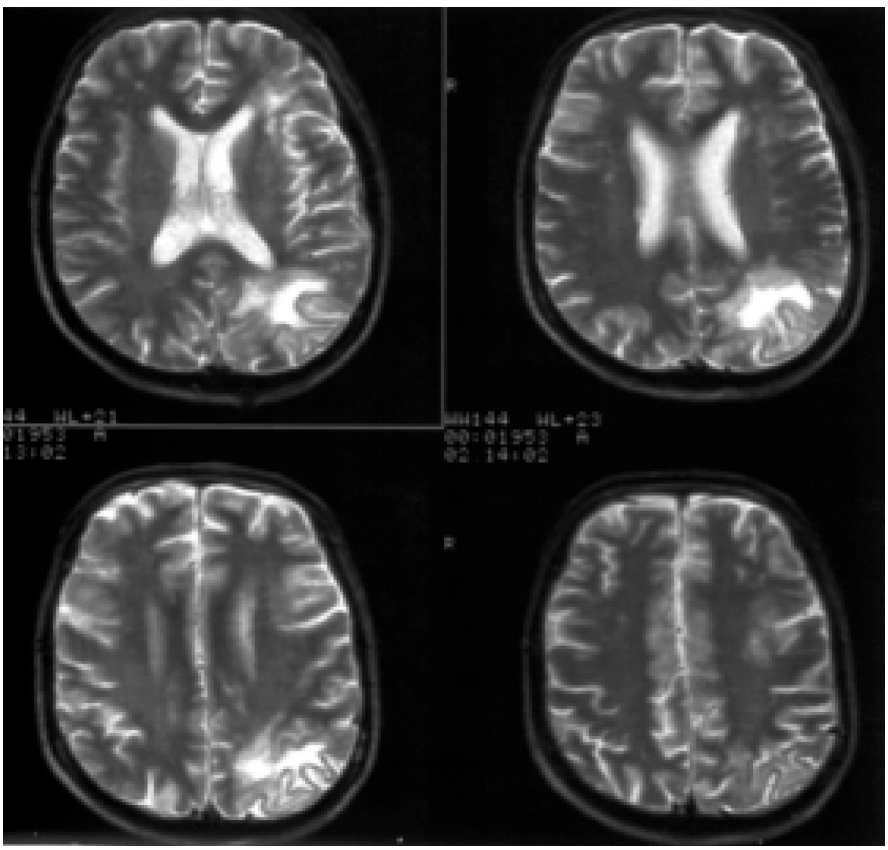

Fig 3. Focal brain lesion of toxoplasmosis.

Cryptococcus

Cryptococcus neoformans is an encapsulated, round-to-oval yeast measuring 4–6 microns with a surrounding polysaccharide capsule ranging in size from 1 to >30 microns when cultivated in the laboratory. In its natural environment, it is smaller and poorly encapsulated.

Cryptococcosis is the cause of the most common life-threatening meningitis in AIDS. Early in the epidemic about 5–8% of patients with AIDS developed cryptococcal infection. The incidence of cryptococcosis, along with other OIs, has decreased where effective antiretroviral treatment (ART) is available.[15] In fact, the decrease in new cases may have started before the advent of HAART; other data suggest a decline in incidence associated with the more frequent use of azole antifungals.[16]

Clinical features

Meningoencephalitis is the most frequent manifestation of cryptococcosis in HIV-infected individuals. It typically presents as a subacute process characterised by headache, fever and, less often, altered

mental status, but presentations characteristic of either acute or chronic meningitis can occur. Cranial nerve palsies and papilloedema are the most common ocular manifestations in patients with cryptococcal central nervous system (CNS) invasion. Complications of CNS infection include hydrocephalus, motor or sensory deficits, cerebellar dysfunction, seizures and dementia. Focal disease is rarely described. Intracerebral granulomata, referred to as cryptococcomas, may be seen occasionally on computed tomography or magnetic resonance imaging.

Abnormal cerebrospinal fluid (CSF) findings such as pleocytosis, low glucose and high protein concentrations are seen in approximately 40% of patients with AIDS-related cryptococcal meningitis (CM). A low CSF white cell count (<20 cells/μl) is associated with a poor prognosis.

Although pulmonary cryptococcosis is diagnosed less frequently than meningitis in patients with AIDS, the lung is most likely the portal of entry. Cryptococcal pneumonia may be either asymptomatic or symptomatic, with or without evidence of dissemination. It is unclear whether disseminated disease represents a progression or reactivation of pulmonary disease because many patients have no evidence of pulmonary involvement at the time of diagnosis of disseminated disease.

Diagnosis

Diagnosis is confirmed by isolation of cryptococcus from a sterile body site by either histopathological analysis or detection of cryptococcal capsular antigen (CrAg). CrAg in the serum usually is indicative of systemic disease and correlates with fungal burden. A localised cryptococcal infection, such as pulmonary cryptococcosis without lymph node involvement, is not usually associated with a positive serum CrAg; a positive result warrants a search for disseminated disease. CrAg in the CSF is produced locally in the subarachnoid space by the invading yeast and does not represent either active or passive diffusion from the serum into the CNS. Detection of CrAg in either serum or CSF has >95% sensitivity and specificity in the diagnosis of true invasive cryptococcal infection.

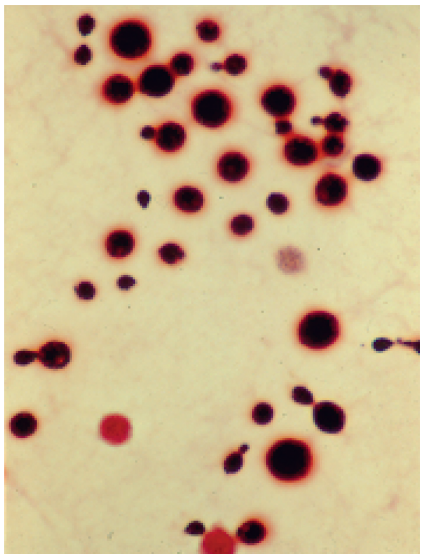

Fig 4. India ink stain outlining the polysaccharide capsule shows positive in 50% of normal hosts and over 80% of AIDS patients.

The India ink stain that outlines the polysaccharide capsule is positive on direct examination of the CSF in approximately 50% of normal hosts with CM and in more than 80% of patients with AIDS (Fig 4). Encapsulated yeasts seen on Alcian blue, mucicarmine or Gomori methenamine silver stains are diagnostic of cryptococcus. Other stains such as Fontana-Masson and periodic acid-Schiff reveal yeast cells but are not specific for cryptococcus.[17]

Treatment

The recommended first-line therapy for AIDS patients with CM is based on the results of the Mycology Study Group (MSG)/AIDS Clinical Trial Group (ACTG) clinical trial: intravenous amphotericin B (0.7 mg/kg per day) plus iv flucytosine (100 mg/kg/day) for two weeks, followed by oral fluconazole (400 mg daily) for eight weeks of consolidation therapy and 200 mg daily for maintenance therapy.[18]

The relapse rates for CM in non-AIDS and AIDS patients are 15–25% and less than 50%, respectively. Prior to the introduction of HAART, patients with AIDS-associated CM had to continue chronic suppressive therapy for the rest of their life. Repeat lumbar punctures (LPs) should be performed after two weeks of therapy; they may also be considered after completion of therapy and at any time there is clinical evidence to suggest relapse. CSF pleocytosis may persist for up to six months after successful treatment, but most patients should have normal CSF findings by one-year post-treatment.

Raised intracranial pressure occurs in more than 50% of cases and may complicate the management. The opening pressure should always be recorded at LP and if this exceeds 20 cm of water, LP should be repeated daily to reduce it to below 20 cm. Insertion of a lumbar drain may be required occasionally.

The US Public Health Service/Infectious Diseases Society of America guidelines recommend discontinuation of secondary prophylaxis if patients:

- successfully complete a course of initial therapy for cryptococcosis
- remain asymptomatic with respect to signs and symptoms of cryptococcosis
- have a sustained increase (>6 months) in their CD4 counts to over 100–200 cells/μl on ART.

Prophylaxis should be restarted if the CD4 count declines to below 100–200 cells/μl.[19]

References

1 Dybul M, Fauci AS, Bartlett JG *et al.* Panel on Clinical Practices for Treatment of HIV. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents. *Ann Intern Med* 2002; 137(5 Pt 2):381–433.

2 Masur H, Ognibene FP, Yarchoan R *et al.* CD4 counts as predictors of opportunistic pneumonias in human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1989;111:223–31.

3 Murray JF, Felton CP, Garay SM *et al.* Pulmonary complications of the acquired immunodeficiency syndrome. Report of a National Heart, Lung, and Blood Institute workshop. *N Engl J Med* 1984;310:1682–8.

4 Kaplan JE, Hanson D, Dworkin MS *et al.* Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2000;30(Suppl 1):S5–14.

5 Wachter RM, Luce JM, Turner J, Volberding P, Hopewell PC. Intensive care of patients with the acquired immunodeficiency syndrome. Outcome and changing patterns of utilization. *Am Rev Respir Dis* 1986;134:891–6.
6 Ong EL, Hanley SP, Mandal BK. Bronchial responsiveness in AIDS patients with *Pneumocystis carinii* pneumonia. *AIDS* 1992;6:1331–3.
7 Rankin JA, Collman R, Daniele RP. Acquired immune deficiency syndrome and the lung. *Chest* 1988;94:155–64.
8 Homer KS, Wiley EL, Smith AL *et al.* Monoclonal antibody to *Pneumocystis carinii*. Comparison with silver stain in bronchial lavage specimens. *Am J Clin Pathol* 1992;97:619–24.
9 Wharton JM, Coleman DL, Wofsy CB *et al.* Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A prospective randomized trial. *Ann Intern Med* 1986; 105:37–44.
10 Bozzette SA, Sattler FR, Chiu J *et al.* A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med* 1990;323:1451–7.
11 Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. Review. *Clin Infect Dis* 1992;15:211–22.
12 Schnapp LM, Geaghan SM, Campagna A *et al. Toxoplasma gondii* pneumonitis in patients infected with the human immunodeficiency virus. *Arch Intern Med* 1992;152:1073–7.
13 Dannemann B, McCutchan JA, Israelski D *et al.* Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. *Ann Intern Med* 1992; 116:33–43.
14 Torre D, Casari S, Speranza F *et al.* Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. *Antimicrob Agents Chemother* 1998;42:1346–9.
15 Murphy EL, Collier AC, Kalish LA *et al.* Viral Activation Transfusion Study Investigators. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. *Ann Intern Med* 2001;135:17–26.
16 Hajjeh RA, Conn LA, Stephens DS *et al.* Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. *J Infect Dis* 1999;179: 449–54.
17 Saag MS, Graybill RJ, Larsen RA *et al.* Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis* 2000; 30:710–8.
18 van der Horst CM, Saag MS, Cloud GA *et al.* Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med* 1997;337:15–21.
19 Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK; CDC; National Institutes of Health; Infectious Diseases Society of America. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR Recomm Rep* 2004;53(RR–15):1–112.