Perspective

Diagnosis, Treatment, and Prevention of Selected Common HIV-Related Opportunistic Infections in the Caribbean Region

The Caribbean region, like other resource-limited areas, lacks many of the diagnostic and treatment modalities taken for granted in richer areas of the world. The Caribbean Guidelines for the Treatment of Opportunistic Infections in Adults and Adolescents Infected With the Human Immunodeficiency Virus provides guidelines for the region for preventing and treating more than 20 opportunistic diseases reflecting the variable availability of diagnostic and treatment resources. Elements of diagnosis and prevention of tuberculosis, Pneumocystis jiroveci *pneumonia, and other common opportunistic conditions in this resource-limited setting were discussed by Jonathan E. Kaplan, MD, at the first CHART Caribbean Conference on the Clinical Management of HIV/AIDS in Montego Bay, Jamaica, in June 2004.*

The Caribbean region, like other resource-limited areas, lacks many of the diagnostic and treatment modalities taken for granted in richer areas of the world. Polling of the attendees at the first CHART Caribbean Conference on the Clinical Management of HIV/AIDS (almost 350 HIV clinicians from 29 countries in the Caribbean region) indicated that approximately one third had access to both computed tomography (CT) and magnetic resonance imaging (MRI), whereas approximately one third had neither; only 10% had access to cryptococcal antigen testing; approximately one fifth reported having the ability to diagnose *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP), which requires induced sputum collection or bronchoscopy to obtain bronchioalveolar lavage specimens, as well as appropriate laboratory staining techniques; and approximately one half did not have access to CD4 + cell count testing.

The *Caribbean Guidelines for the Treatment of Opportunistic Infections in Adults and Adolescents Infected with the Human Immunodeficiency Virus*, presented at the conference, represents a prodigious effort on the part of the Caribbean HIV-care community and offers invalu-

able regional guidelines for preventing and treating more than 20 opportunistic infections (OIs). The guidelines are oriented toward diagnosis and treatment of specific OIs. However, a syndromic approach to diagnosis and treatment of OIs is critical in assessing HIV-infected patients in settings in which laboratory diagnostics are lacking. Many of the OIs occurring in HIV-infected individuals are signaled by symptoms or signs that should prompt suspicion for specific conditions. The syndromic approach is represented in the acute care module of the World Health Organization (WHO)

Integrated Management of Adolescent and Adult Illness modules. (The 4 modules of this program—acute care, chronic HIV care with antiretroviral treatment, general principles of good chronic care, and palliative care—are available at www.who.int/3by5/publications/documents/imai/en/.) The acute care module covers all common illnesses, but gives particular attention to those associated with HIV infection. It was specifically prepared to be used in peripheral health centers with limited or no laboratory diagnostics and where care may be provided by nurses and physician assistants.

Diagnosis of Opportunistic Infections

Tuberculosis

The natural history of HIV disease is such that most OIs occur after the CD4 + cell count has decreased to below 200/μL (Figure 1). Tuberculosis (TB) can occur at any CD4 + cell count. The pres-
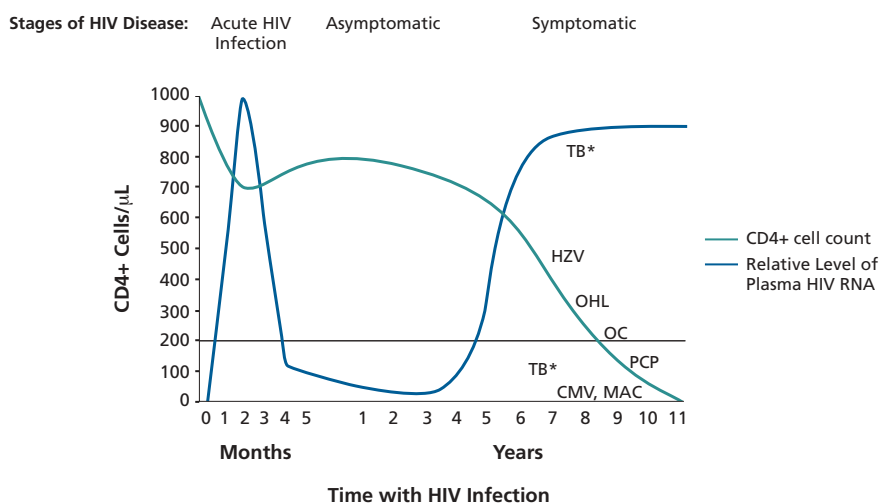

Figure 1. Natural history of HIV infection and common complications. TB indicates tuberculosis (*can occur at any CD4+ cell count); HZV, herpes zoster virus; OHL, oral hairy leukoplakia; OC, oral candidiasis; PCP, *Pneumocystis jiroveci* pneumonia; CMV, cytomegalovirus; MAC, *Mycobacterium avium* complex.

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ence of oral candidiasis is clinically correlated with CD4 + cell counts of 200/μL or less, and infections such as PCP, cytomegalovirus infection, and disseminated *Mycobacterium avium* complex (MAC) disease are seen with progressively lower CD4 + cell counts. There is very little published information regarding the prevalence of opportunistic illnesses in HIV-infected populations in the Caribbean. One published report in a small number of patients from Haiti indicated that TB was the most common AIDS-defining condition, having been the index diagnosis in 39% of patients (Table 1).

Table **1**. Prevalence of AIDS-Defining Conditions Among 23 Persons with AIDS in Haiti

	Prevalence
Tuberculosis	39%
Wasting syndrome	31%
CD4+ count <200 cells/μL	10%
Cryptosporidiosis	4%
Cyclospora diarrhea	4%
Cryptococcal meningitis	4%
Candida esophagitis	4%
Toxoplasmosis	4%

Data from Deschamps, *AIDS,* 2000.

Figure 2 (color figures appear on pages 138 and 139) shows the x-ray of a young HIV-seropositive man who presented with fever and cough of 4 weeks' duration. The x-ray findings illustrate the atypical presentation of TB in HIV-infected individuals compared with that in HIV-uninfected individuals. The apical infiltrates or cavitation characteristic of TB in nonimmunosuppressed patients frequently are absent in HIV-infected patients, in whom the chest radiographic findings may be quite variable. The diagnostic sputum acid-fast smear showing tubercle bacilli is shown in Figure 2.

TB causes 11% of HIV-related deaths worldwide. As noted, it can occur at any CD4 + cell count. The clinical presentation of the disease becomes increasingly atypical as CD4 + cell count declines, with the x-ray picture becoming increasingly difficult to distinguish from that of

other pulmonary conditions, and extrapulmonary manifestations of infection becoming more common. In resource-limited areas, a significant percentage of newly diagnosed HIV-infected individuals are found to have active TB. There are some data from Africa indicating that 5% to 10% of patients have active TB at the time of diagnosis of HIV infection. *TB should always be considered in an HIV-infected person with a pulmonary infiltrate.*

PCP

Figure 3 shows the x-ray of another young man with HIV infection who presented with fever and a nonproductive cough of 2 to 3 weeks' duration. The bilateral interstitial infiltrates shown are indicative of PCP; the organism is shown using methenamine silver stain of a bronchioalveolar lavage specimen. PCP is characterized by subacute onset (days to weeks) of shortness of breath, dry cough, and fever. The shortness of breath can be quite marked and may appear to be inconsistent with the findings on chest x-ray. Physical examination shows tachypnea and frequently hypoxemia, although the chest exam may reveal no adventitious sounds (rales or rhonchi). As noted, chest x–rays show bilateral, diffuse, interstitial pulmonary infiltrates. Diagnosis in resource-limited areas is difficult since it requires bronchoscopy or induced sputum and special stains that are not available in most laboratories. A normal sputum specimen is not sufficient for diagnosis. Treatment of choice is trimethoprim/sulfamethoxazole 15 to 20 mg/kg/ day for 3 weeks. In severe cases, prednisone 40 mg twice a day with dose tapering over 3 weeks can be given. However, use of prednisone is highly problematic in areas in which a definitive diagnosis of PCP cannot be made, since TB should be suspected in all patients with pulmonary infiltrates and prednisone should not be given to individuals with active TB. After successful initial treatment, chronic maintenance therapy is required, usually consisting of trimethoprim/sulfamethoxazole 160/800 mg/day.

Bacterial Pneumonia

Figure 4 shows the lobar infiltrate characteristic of acute bacterial pneumonia and the sputum gram stain showing polymor-

phonuclear leukocytes and gram-positive diplococci. Onset of acute bacterial pneumonia is rapid (1 to a few days) and features fever and productive cough. It is important to recognize that bacterial pneumonias are about 8 times more common in HIV-infected persons than in HIV-uninfected persons, with pneumococcal bacteremia about 100 times more common. Bacterial pneumonia can occur at any CD4 + cell count, with common causative agents including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Treatment consists of penicillin/ampicillin with or without an aminoglycoside or a third-generation cephalosporin.

Cryptococcal Meningitis

Figure 5 is an India ink preparation of spinal fluid showing the yeast form of *Cryptococcus neoformans* with the characteristic capsule around the organism. The sample was from a patient who presented with fever and complained of a progressively increasing headache over 2 weeks, which was described as extremely severe. This is a typical physical presentation of cryptococcal meningitis, with patients often describing the headache as the worst they have ever experienced. Mental disturbance is frequently present and increases in degree as disease worsens. As with other forms of meningitis, there generally are no focal neurologic signs on physical exam, allowing some degree of differentiation from conditions associated with focal abnormalities, such as toxoplasmic encephalitis and non-Hodgkin's lymphoma. The differential diagnosis principally involves bacterial meningitis and tuberculous meningitis. Lumbar puncture typically shows high opening pressure, and reducing the increased intracranial pressure constitutes an important aspect of managing patients with this infection. Protein levels are usually elevated, and approximately half of patients have low glucose levels.

The causative organisms can be isolated from the spinal fluid. Traditionally, the India ink method has been considered somewhat insensitive, with diagnosis relying on cryptococcal antigen testing; however, the sensitivity of the India ink method is likely markedly increased in patients with AIDS, who typically have large numbers of organisms, and the method is both relatively inexpensive
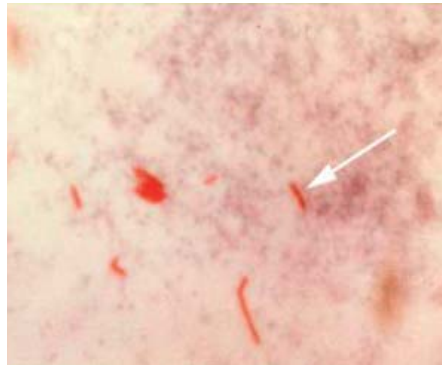
Figure **2.** Chest x-ray in a patient presenting with fever and cough of 4 weeks' duration (left). Acid-fast smear of sputum shows tubercle bacilli (right). This x-ray is illustrative of atypical findings of pulmonary tuberculosis in HIV-infected individuals.
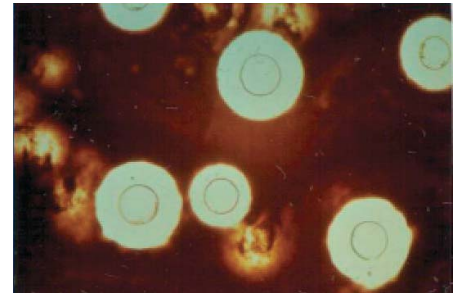

Figure **5.** India ink preparation of spinal fluid showing the yeast form of *Cryptococcus neoformans* with the characteristic capsule around the organism. Organisms were observed in a patient with cryptococcal meningitis who presented with fever, increasingly severe headache, and no focal neurologic signs.
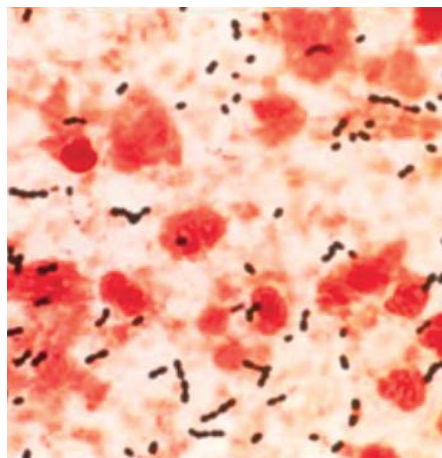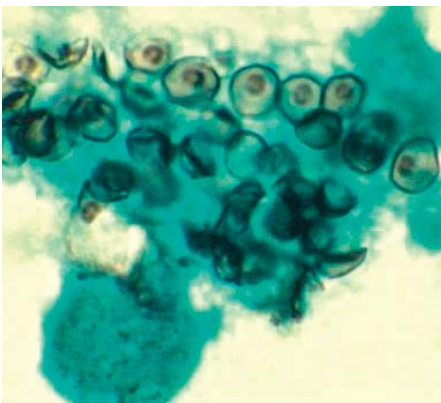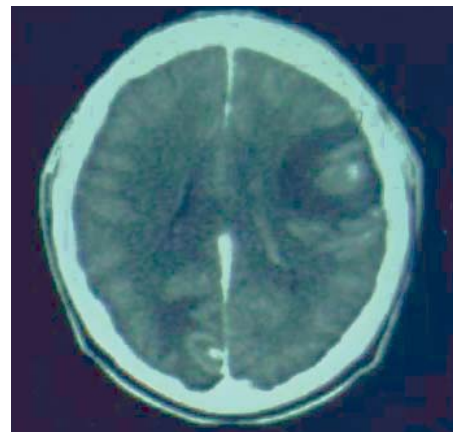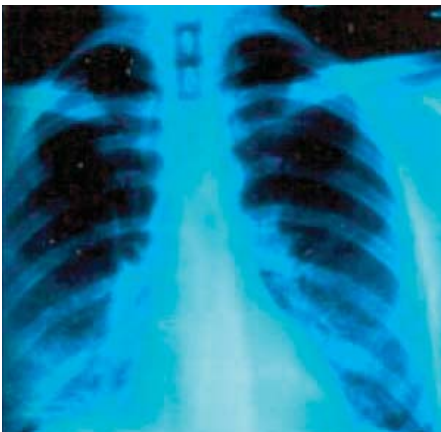

Figure **3.** Chest x-ray in a patient presenting with fever and nonproductive cough (top). Methenamine silver staining of a bronchioalveolar lavage specimen shows *Pneumocystis jiroveci* (PCP) (bottom). X-ray findings in PCP characteristically consist of bilateral, diffuse, interstitial pulmonary infiltrates.

Figure **4.** Chest x-ray shows the lobar infiltrate characteristic of acute bacterial pneumonia (top), with sputum gram stain showing polymorphonuclear leukocytes and gram-positive diplococci (bottom).

Figure **6.** Computed tomography scan of patient presenting with fever, headache, motor weakness, and recent seizure—a presentation suggestive of a focal neurologic lesion. The blank area around the lesion is edema. Multiple focal lesions are characteristic of cerebral toxoplasmosis.
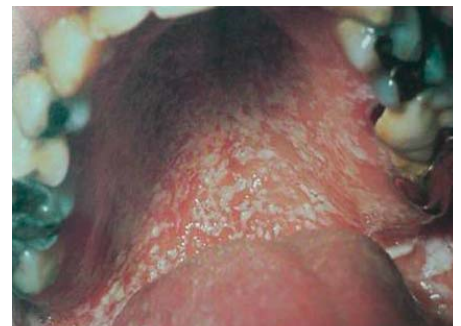
Figure **7.** Oral candidiasis (thrush). Appearance of oral candidiasis is a good clinical correlate of advanced immunosuppression. Physical exam should always include the mouth.
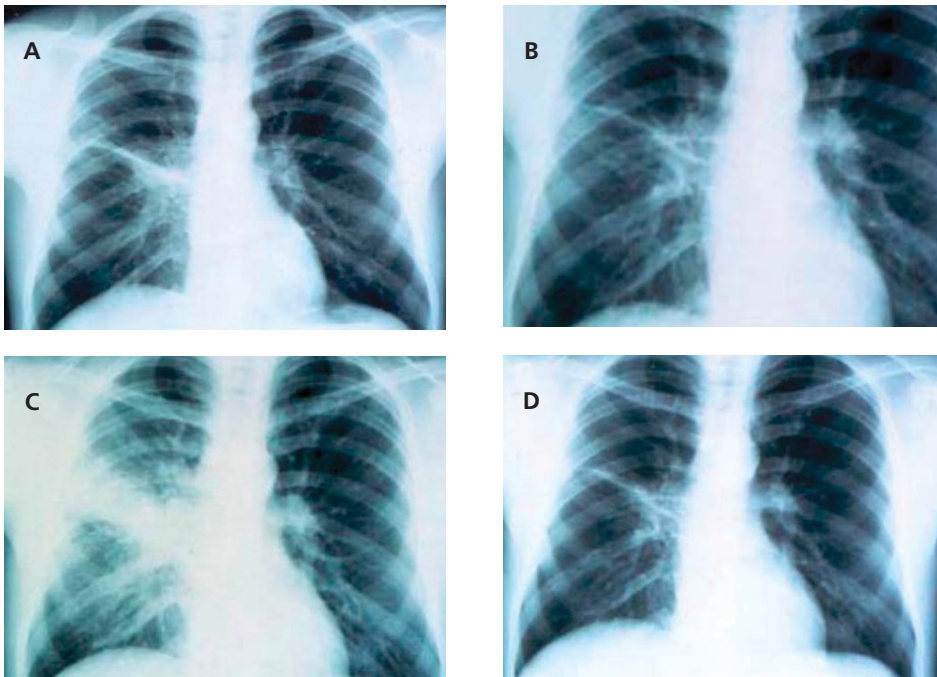
Figure 8. (A) Initial chest x-ray of patient with tuberculosis shown in Figure 2. (B) Improvement after 1 month of 4-drug antituberculosis therapy. (C) After 1 month of potent antiretroviral therapy; apparent worsening of disease reflects increased inflammatory response associated with immune reconstitution under antiretroviral therapy. (D) One month later, after response to antiinflammatory medication.

and more readily available. High-dose fluconazole can be used to treat mild cases of infection. However, patients with mental status deterioration require amphotericin treatment for 2 weeks, followed by fluconazole for 8 to 10 weeks. It is ideal to combine amphotericin with flucytosine for the initial 2 weeks of treatment, since the combination treatment yields a lower relapse rate. However, flucytosine is variably available in many resource-limited areas. Chronic maintenance therapy consisting of fluconazole 200 mg/day must be given after successful treatment.

Toxoplasmosis

Figure 6 shows a CT scan of a patient presenting with fever and headache; the patient also had some motor weakness and a recent seizure, suggesting a focal neurologic lesion. The CT scan shows a typical toxoplasmosis lesion, with a ring-enhancing pale or blank area around the lesion. Although this area of edema is suggestive of toxoplasmosis, it is not diagnostic, since such edema may conceivably be present with other focal lesions (eg, lymphoma). The defining characteristic in imaging of toxoplasmosis is the

presence of multiple focal lesions (not shown in Figure 6). As with the presentation of the current patient, findings in cerebral toxoplasmosis include headache, fever, confusion, and motor weakness, with focal neurologic signs on physical exam. Diagnosis is made by the finding of multiple mass lesions on CT or MRI. Treatment consists of pyrimethamine, sulfadiazine, and folinic acid for 8 weeks; chronic maintenance therapy is performed with the same regimen after successful treatment.

Oral Candidiasis

Practitioners in the Caribbean are likely very familiar with the appearance of oral candidiasis, or thrush (Figure 7). Diagnosis can be made visually; the white plaques can be lifted off with a tongue blade. Oral candidiasis is a reliable marker of advanced immunosuppression, emphasizing the importance of examining the mouth in all patients. There are many treatments for oral candidiasis, including clotrimazole troches (10 mg 5 times a day for 7 days), nystatin, and gentian violet, as well as fluconazole. For esophageal candidiasis, fluconazole should be given at 3 to 6

mg/kg/day for 2 weeks. It is suggested that maintenance therapy with fluconazole 200 mg/day be continued for several months after successful treatment.

Immune Reconstitution Syndromes

Figure 8 represents a phenomenon that is likely to be seen with increasing frequency as effective antiretroviral therapy becomes more widely available worldwide. Figure 8A shows the chest x-ray of the young man with TB previously discussed at presentation, and Figure 8B shows the changes after 1 month of 4-drug therapy for TB. At that point, the patient was clinically and radiologically improved, and the decision was made to start triple-drug antiretroviral therapy and to continue the TB regimen. After 1 month, the patient complained of fatigue and general malaise. Another chest x-ray was taken at that time (Figure 8C), showing changes that might reflect worsening of the TB due to nonadherence to medication, emergence of drug-resistant TB, or superinfection. However, the patient actually was experiencing an immune reconstitution reaction under antiretroviral therapy, characterized by increased immune system activation and inflammatory response to the tubercle bacilli in the lung, even though most of the organisms were probably dead at this time. The patient's clinical picture did not match the severity of illness suggested by the chest x-ray in that he was not complaining of much shortness of breath. He started antiinflammatory medication, to which he responded; 1 month later, the patient was doing quite well and the inflammatory response had resolved (Figure 8D).

In addition to the so-called "paradoxical reaction" occurring under antiretroviral therapy in patients with TB, immune reconstitution syndromes have been observed with a number of other opportunistic conditions, whether previously diagnosed or not, usually within 2 to 6 weeks after starting potent antiretroviral therapy. Such syndromes have been observed for MAC disease, PCP, toxoplasmosis, hepatitis B virus infection, hepatitis C virus infection, cytomegalovirus infection, varicella-zoster virus infection, cryptococcosis, and progressive multifocal leukoencephalopathy. These immune reconstitution syndromes can be expected to occur with greater frequency as antiretroviral therapy becomes more
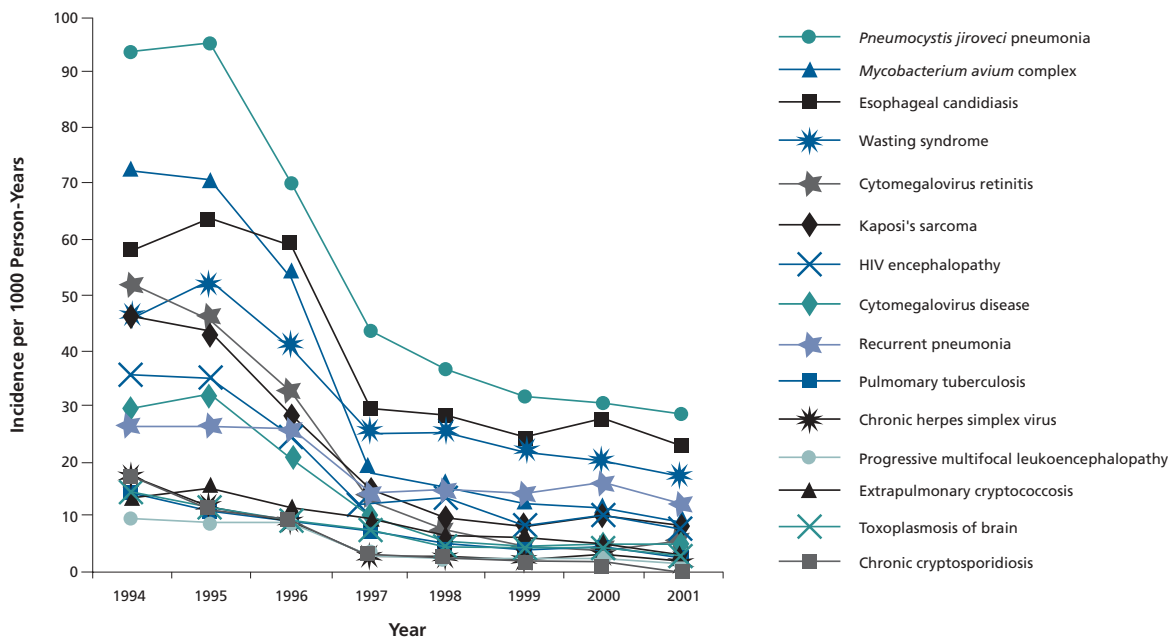
Figure 9. Incidence of the 15 most common opportunistic illnesses from 1994 to 2001 in the Centers for Disease Control and Prevention's Adult and Adolescent Spectrum of HIV Disease Project. Adapted from Wolfe et al, Natl HIV Prev Conf, 2003.

widely available in resource-limited regions.

Prevention of OIs

Figure 9 shows the incidence of the 15 most common opportunistic illnesses in the United States between 1994 and 2001. The advent of triple-drug antiretroviral therapy in 1995 to 1996 brought sharp declines in the incidence of these illnesses, including both those for which there is effective prophylaxis and those for which there is not. The point to be gleaned in terms of prevention is that antiretroviral therapy is the most potent preventive regimen available against opportunistic illnesses. However, there are many specific interventions against OIs that are effective, that have been shown to reduce morbidity and mortality even in the setting of antiretroviral therapy, and that therefore remain important in the antiretroviral treatment era, particularly in those areas of the world that do not have access to antiretroviral drugs. Preventable illnesses include PCP, cerebral toxoplasmosis, TB, MAC disease, and disease caused by *S pneumoniae*.

The survival benefit of PCP prophylaxis was demonstrated in the late 1980s, and the recommendation for trimethoprim/sulfamethoxazole prophylaxis against PCP was made in 1989. In the early 1990s, it was often considered to be the single most important drug available in the HIV armamentarium because of its effectiveness in PCP prevention. The current eligibility criteria for PCP prophylaxis consist of CD4+ count below 200 cells/μL (or CD4+ cell percentage below 14%) or a history of oral candidiasis. In resource-limited areas where CD4+ cell count or percentage testing is not available, criteria may need to include other markers for advanced immunosuppression, such as WHO stage 4 clinical disease or total lymphocyte count below 1200/μL. The regimen of choice is trimethoprim/sulfamethoxazole 160/800 mg (1 double-strength tablet) once daily; if it is not tolerated, other drugs are available for prophylactic use. Trimethoprim/sulfamethoxazole prophylaxis is also recommended for HIV-exposed or –infected children aged 1 to 12 months and in older HIV-infected children with CD4+ cell percentage below 15%. There is a peak incidence of PCP in HIV-infected children at 3 to 6 months of age, prior to the age at which HIV infection may be diagnosed.

Trimethoprim/sulfamethoxazole is a powerful agent to have in the armamentarium. In addition to being an effective prophylaxis against PCP, it can also prevent cerebral toxoplasmosis, disease caused by *S pneumoniae*, disease caused by nontyphoid *Salmonella*, nocardiosis, isosporiasis, and malaria. This drug has a number of other advantages. It is inexpensive (US$1 per month) and easy to administer. The only contraindication to its use is history of sulfa allergy. The main adverse reaction is skin rash, and this has been found to be relatively uncommon in dark-skinned persons. Clinical rather than laboratory monitoring of therapy appears to be adequate. Adherence is not as critical as for antiretroviral therapy, as the missing of a dose or doses basically equals the loss of some efficacy. Finally, experience with taking a daily medication is good preparation and practice for taking daily antiretroviral therapy regimens.

Diagnosis, prevention, and treatment of TB was discussed more fully in the presentation by Jean William Pape, MD (also summarized in this issue of *Topics in HIV Medicine*). In brief, the WHO has formulated international "best practice" guidelines for use of isoniazid preventive therapy (IPT). If skin testing is available, IPT may be reserved for persons with a positive tuberculin skin test (≥5 mm induration in HIV-infected persons). Otherwise, it is suggested that all HIV-seropositive patients living in countries with a high prevalence of TB receive IPT. It is also suggested that HIV-seropositive persons exposed to a case of active TB receive IPT. Exclusion of active TB is imperative prior to initiating isoniazid prophylaxis, since administration of a

single drug to a person with active TB will likely result in antimicrobial resistance. The regimen for IPT is isoniazid 300 mg/day for 9 months. Isoniazid prophylaxis is also recommended for HIV-infected children exposed to a person with active TB.

Immune reconstitution under antiretroviral therapy can enable prophylaxis for OIs to be discontinued in some cases. In the absence of immune reconstitution, several forms of prophylaxis should be continued for life, including primary prophylaxis against PCP and secondary prophylaxis (chronic maintenance therapy) following successful treatment of PCP, cerebral toxoplasmosis, systemic (deep) fungal infections (eg, cryptococcosis, histoplasmosis), disseminated MAC infection, and cytomegalovirus disease.

Suggested Reading

Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among HIV-infected persons: 2002 recommendations of the US Public Health Service and the Infectious Diseases Society of America. *MMWR Morb Mortal Wkly Rep.* 2002;51(RR-8):1-52.

Centers for Disease Control and Prevention. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR Morb Mortal Wkly Rep.* 2004;53(RR-14):1-42.

Centers for Disease Control and Prevention. 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 Morb Mortal Wkly Rep.* 2004;53(RR-15):1-112.

Deschamps MM, Fitzgerald DW, Pape JW, Johnson WD. HIV infection in Haiti: natural history and disease progression. *AIDS.* 2000;14:2515-2521.

Grant AD, Kaplan JE, DeCock KM. Preventing opportunistic infections among human immunodeficiency virus-infected adults in African countries. *Am J Trop Med Hyg.* 2001;65:810-821.

Wolfe MI, Hanson DL, McNaghten AD, Teshale EH, Aponte Z, Sullivan PS. The changing spectrum of HIV disease in the United States—data from the Adult Spectrum of Disease Project. [Presentation T1-B0204.] National HIV Prevention Conference. July 27-30, 2003; Atlanta, Ga.