

Perspective

HIV-Related Opportunistic Infections Are Still Relevant in 2015

The incidence of HIV-related opportunistic infections (OIs) has declined in the United States with the increasing use of effective antiretroviral therapy for the treatment of HIV infection. However, the absolute number of patients with OIs remains high and there continues to be considerable associated mortality. OI guidelines from the National Institutes of Health, Centers for Disease Control and Prevention, and Infectious Diseases Society of America continue to be updated on a regular basis, several times per year, as optimal strategies for prevention and therapy evolve. Recommendations that have changed in these guidelines include: screening for cryptococcal antigen and treatment of asymptomatic antigenemia; empiric treatment of shigellosis infection in light of the recent spread of multidrug-resistant strains; the relative roles of vancomycin and metronidazole in diarrheal illness related to Clostridium difficile; and diagnosis of Pneumocystis jiroveci pneumonia (PCP; formerly Pneumocystis carinii pneumonia). This article summarizes a presentation by Henry Masur, MD, at the IAS–USA continuing education program held in Washington, DC, in May 2015.

Keywords: HIV, opportunistic infections, cryptococcal meningitis, shigellosis, Clostridium difficile, Pneumocystis jiroveci pneumonia

With the remarkable prolongation of life achieved among HIV-infected individuals, owing to the use of potent antiretroviral therapy, has come dramatic progress in reducing the incidence of HIV-related opportunistic infections (OIs). There has been considerable focus on antiretroviral therapy and HIV prevention, and most HIV practitioners are highly proficient at managing antiretroviral therapy. However, expertise in the management of OIs has waned as more and more physicians have little experience diagnosing or treating these life-threatening infections. Renewed attention to appropriate management is needed, because the absolute number of patients with OIs and the rates of associated mortality remain high, particularly in large urban settings in the United States.

Updates to the OI guidelines have been released online by the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA).¹ The following covers topics under discussion during preparation of these guidelines.

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Cryptococcal Disease

There are nearly a million cases of cryptococcal meningitis worldwide each year, with an estimated annual death toll of 675,000.^{2,3} It has been suggested that in parts of the world with high burdens of disease, it is cost-effective to routinely screen asymptomatic patients for cryptococcal antigen.

As shown in Figure 1, a study in a cohort of 707 South African individuals showed that even when CD4+ cell count increased during the first year of antiretroviral therapy, there was still an appreciable incidence of cryptococcal meningitis during this initial year of antiretroviral therapy.⁴ This high incidence reflects a population that is nonadherent to or has a poor response to antiretroviral therapy, but also indicates that OIs can occur within the first few weeks or months after initiation of antiretroviral therapy. Such episodes may represent primary cryptococcal infection, relapsed infection, re-infection, or some manifestation of immune reconstitution inflammatory syndrome (IRIS).

Thus, starting antiretroviral therapy does not guarantee prevention of cryptococcal meningitis. Although the incidence of cryptococcal disease is much higher in sub-Saharan Africa than in the United States, the issues of screening for asymptomatic infection and treating in the United States are still important even if the incidence is lower than in other geographic areas.

In the South African study mentioned above, 7% of individuals screened before starting antiretroviral therapy had asymptomatic cryptococcal antigenemia, while in a study in the United States approximately 2.0% to 2.5% of individuals

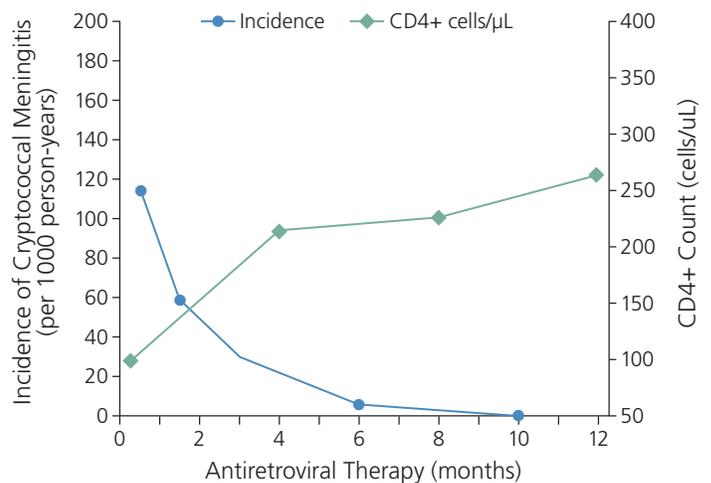


Figure 1. Incidence of cryptococcal meningitis among 707 South African individuals during their first year of antiretroviral therapy. Adapted from Jarvis et al.⁴

starting antiretroviral therapy had it.^{4,6,7} A cryptococcal antigen titer result greater than or equal to 1:8 was 100% sensitive and 96% specific for predicting cryptococcal meningitis during the first year of antiretroviral therapy in those with no history of the disease. Only 56% of those who tested positive for cryptococcal antigen cleared their antigenemia with antiretroviral therapy alone.⁷ A short course of low-dose fluconazole was not effective in preventing meningitis. Thus, treatment for individuals with antigenemia should consist of a relatively high dose of fluconazole, as would be used to treat meningitis, or an alternative such as amphotericin B.

World Health Organization recommendations for resource-limited settings with a high burden of cryptococcal disease are to screen all HIV-seropositive patients with CD4+ cell counts below 100/ μ L for cryptococcal antigen and to treat patients with antigenemia with fluconazole 800 mg daily for 2 weeks and 400 mg daily for 8 weeks. Although logical and plausible, these treatment recommendations are not based on clinical evidence.⁵ Should practitioners follow these recommendations in the United States?

The findings in South Africa and in other resource-limited areas have prompted questions about the number of events of acute meningitis that represented IRIS rather than acute fungal disease, about whether lumbar punctures could have been used to distinguish between patients with antigenemia who did need therapy and those who did not need therapy, and about whether therapy with fluconazole would have changed outcomes.

Prior to 2015, the NIH/CDC/IDSA OI guidelines stated that for prevention of cryptococcal disease, screening for cryptococcal antigenemia was not recommended because of the low incidence of cryptococcal disease among HIV-infected individuals after initiation of antiretroviral therapy. However, recent data indicate that the burden of cryptococcal disease is probably more substantial in the United States than many clinicians suspect. As reported by McKenney and colleagues in *Morbidity and Mortality Weekly Report* in 2014 and in *Clinical Infectious Diseases* in 2015, the attack rate of cryptococcal meningitis among HIV-infected persons in the United States for 2006 was 2 to 7 cases per 1000 person-years, with a 12% rate of associated mortality.^{6,7}

McKenney and colleagues also evaluated the prevalence of asymptomatic cryptococcal antigenemia using stored sera from the MACS (Multicenter AIDS Cohort Study) and WIHS (Women's Interagency HIV Study) cohorts from 1996 to 2012. Among 1872 samples with CD4+ cell counts below 100/ μ L, 2.9% were positive for cryptococcal antigen, including 4.6% of samples with CD4+ cell counts below 50/ μ L. There was a wide range of antigen titers. A minority of cases of antigenemia were associated with prior cryptococcal meningitis. It is unknown if any of the individuals whose samples were evaluated received treatment for active cryptococcal disease or for asymptomatic antigenemia. Survival was shorter in antigen-positive individuals compared with antigen-negative individuals (Figure 2).⁷ The investigators concluded that the prevalence of asymptomatic cryptococcal antigenemia is substantial in the United States, that survival rates are worse for

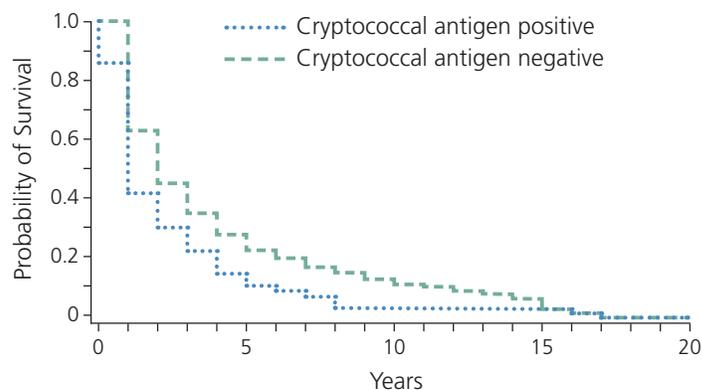


Figure 2. Survival according to cryptococcal antigen test result in MACS (Multicenter AIDS Cohort Study) and WIHS (Women's Interagency HIV Study) cohorts, from 1986 to 2012. Adapted from McKenney et al.⁷

individuals with antigenemia, and that specific therapy for cryptococcal disease in those with antigenemia is warranted.

In the United States, cryptococcal antigenemia is more common than many may have recognized. Data suggest that antiretroviral therapy is not uniformly effective for preventing cryptococcal syndromes from occurring. When is treatment for cryptococcal disease indicated? Some clinical syndromes may in fact be caused by the unmasking effects of IRIS or by reactivity to latent or cured disease. However, clinicians may be reluctant to assume that live organisms and active infection are absent.

Treatment for meningitis would be indicated in cases in which a lumbar puncture yields a positive culture from cerebrospinal fluid. Patients with meningeal disease can receive the same treatment as patients with pulmonary disease. A reasonable interpretation of available data supports screening all individuals with CD4+ cell counts below 100/ μ L for cryptococcal antigen and performing a lumbar puncture in antigen-positive individuals to identify active but asymptomatic meningitis. For patients who have cryptococcal meningitis, even if it is clinically silent, treatment should follow current guidelines (ie, should start with liposomal amphotericin B plus flucytosine). If a lumbar puncture result is negative for meningitis and there is no evidence of organ dysfunction, treatment with fluconazole is encouraged.

Diarrhea

Diarrhea is common in many individuals, including those with HIV infection, and many cases of diarrhea can be attributed to common infectious and noninfectious causes. However, clinicians should be aware that *Clostridium difficile* is also a common cause of diarrhea among HIV-infected persons. Although *C difficile* is not an opportunistic pathogen, it does occur frequently in HIV-infected individuals, presumably because of their regular interaction with health-care facilities. Clinicians should also be aware of changes in the antibiotic susceptibility patterns of enteric bacteria that often infect HIV-infected individuals.

Salmonella infection is a well-known HIV-related OI that frequently causes bacteremia, especially in individuals who live in the developing world. *Campylobacter* and *Shigella* infections are common in many populations, although they are not OIs. However, because these infections also occur in HIV-infected individuals and because men who have sex with men (MSM) have a particular predisposition to shigellosis, some of the new data on antimicrobial susceptibility and enteric pathogens are relevant to HIV practitioners.

Shigellosis

Approximately 500,000 cases of shigellosis occur each year in the United States among the total population of HIV-infected and uninfected individuals. Transmission of *Shigella* species occurs via person-to-person contact or via food and water and can be achieved with a low inoculum of 10 to 100 organisms. *Shigella* species are relatively resistant to stomach acid. Secondary cases of shigellosis are common (ie, spread from one infected person to another). In April 2015, Bowen and colleagues reported in *Morbidity and Mortality Weekly Report* that shigellosis with multidrug resistance, including resistance to quinolones, is spreading in the United States, particularly among MSM.⁸ Numerous other reports on the drug-resistant bacteria have appeared in popular press and media.

For individuals with persistent diarrhea, empiric treatment for shigellosis is reasonable if diarrhea is severe, with stools that occur more than 6 times a day, with bloody stools, or if a high fever is present. Because transmissibility is a concern, treatment for shigellosis among MSM to potentially reduce the period of infectivity should also be considered.

A 7- to 10-day regimen of quinolone treatment is the preferred empiric therapy option for treatment of shigellosis. However, *Shigella* species are becoming increasingly resistant to quinolones in the United States and abroad. The most resistant strain is *Shigella sonnei*, which is common among travelers and increasingly common among MSM. Treatment options in cases of resistance are limited. Individual antibiograms should be studied to determine if azithromycin, trimethoprim-sulfamethoxazole, or another agent should be selected. *Campylobacter* species infection, another common cause of diarrhea, is also becoming resistant to quinolones.

Clostridium difficile

Clostridium difficile infection is reported to be the most common identified cause of diarrhea in HIV-infected individuals, accounting for 55% of cases in one study, especially those who acquired it in health-care facilities and in association with antibiotic treatment.⁹ *Campylobacter* and *Shigella (flexneri)* more commonly than *sonnei*) infections each accounted for 14% of cases of diarrhea, *Salmonella* infection accounted for 7% of cases, and mycobacterial infections accounted for 4% of cases.

The clinical manifestations of *C difficile*-related diarrhea are similar in HIV-infected and uninfected individuals. Individuals with low CD4+ cell counts have higher incidence

rates for *C difficile*-associated diarrhea than those with high CD4+ cell counts. However, whether low CD4+ cell counts contribute to a higher incidence of clinically apparent disease or whether individuals with low CD4+ cell counts have a higher incidence of disease owing to more-frequent antibacterial therapy or more-frequent exposure to health-care facilities remains to be determined.

To diagnose *C difficile* as the cause of diarrhea, a nucleic acid amplification test (eg, a polymerase chain reaction [PCR] test) of a stool sample is now preferred by most laboratories. Many laboratories have used enzyme-linked immunosorbent assays (ELISAs). These assays are very specific for toxin but are not very sensitive. Thus, many cases of *C difficile*-related diarrhea are missed by ELISA testing even when 3 consecutive stools are sampled. Nucleic acid amplification tests are also very specific for toxin and their high sensitivity gives them a great negative predictive value. However, they are so sensitive that they may return positive results for *C difficile* in some patients with diarrhea even if only a small amount of toxin is present (potentially too little to cause disease). Thus, a positive PCR test result must be analyzed with caution.

Some laboratories screen stool samples with an antigen test, the lactic dehydrogenase test, to determine the presence of the *C difficile* organism and then use an ELISA test to detect toxin. This is also a reasonable diagnostic approach, although laboratories often resort to a PCR test if the results of stool antigen and ELISA tests are discordant.

A recent analysis of HIV-uninfected patients indicated higher clinical success rates and somewhat lower relapse rates with oral vancomycin than with metronidazole when used to treat mild, moderate, or severe *C difficile* infection.¹⁰ Updated guidelines recommend oral vancomycin over metronidazole to treat all HIV-infected individuals, particularly those with CD4+ cell counts below 200/ μ L.¹ However, metronidazole can be used to treat HIV-infected patients with very mild cases of *C difficile* infection. Although combination therapy is controversial, there are data indicating the benefit of using vancomycin and metronidazole together for severe cases of *C difficile* infection.¹¹

Diagnosis of *Pneumocystis jiroveci* Pneumonia

Clinicians have long sought approaches to diagnosing *Pneumocystis jiroveci* pneumonia (PCP; formerly *Pneumocystis carinii* pneumonia) that do not require bronchoscopy or the evaluation of a respiratory specimen. There has been considerable literature on a variety of serologic tests that are purported to be useful for diagnosis of PCP.

Serum PCR testing is not sensitive enough to be useful diagnostically. Although PCR testing is useful for evaluation of respiratory secretions, as discussed below, it is not useful for evaluation of blood, plasma, or serum. Lactate dehydrogenase testing has been discussed in the literature for 2 decades; however, serum lactate dehydrogenase testing is non-specific (its sensitivity depends on the severity of the lung disease). Serum beta-D-glucan testing has appeared promising

in some reports, but this test measures a component of the cell wall that is present in many fungi, including *Candida* species. Moreover, false-positive results for PCP on beta-D-glucan tests may be caused by noninfectious entities or by fungal contamination of drugs. The use of beta-D-glucan testing has strong proponents, but its lack of specificity and its imperfect sensitivity would make it unreliable even if hospitals were able to obtain the results quickly. Thus, there is currently no useful serologic test for PCP.

With sputum and bronchoalveolar lavage (BAL) specimens, most laboratories establish a diagnosis of PCP by “spinning down” the respiratory specimen to concentrate it and then staining it with a colorimetric or immunofluorescent stain. Such stains are highly specific and sensitive for PCP when interpreted by experienced microscopists. However, many laboratories do not have access to an experienced microscopist and may need to find an automated system to establish the diagnosis of PCP.

PCR testing is nearly 100% specific and sensitive for PCP. The problem with this test is that it detects colonization of *Pneumocystis* organism as well as PCP. A negative result for PCP via BAL PCR testing will rule out PCP; however, a positive result might indicate colonization rather than disease. Therefore, PCR test results must be interpreted with caution. The gold standard for diagnosis of PCP is an immunofluorescent stain of concentrated BAL. Such testing may be done initially or only for those specimens that are positive for PCP by PCR testing. Thus, for both *C difficile* infection and PCP, PCR testing provides a highly sensitive and highly specific testing modality, although such testing may identify colonization in patients whose disease is in fact caused by some other process.

Conclusion

HIV practitioners must still manage OIs in their HIV-infected inpatients and outpatients. The epidemiology and management of OIs continues to evolve and will remain important as long as HIV infection is identified late in the course of illness or for individuals who do not achieve durable HIV suppression. 

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