Perspective

Recurring and Emerging Questions Related to Management of HIV-Related Opportunistic Infections

The incidence of HIV-related opportunistic infections (OIs) has dramatically declined with the ability to achieve viral suppression and immune reconstitution with potent antiretroviral therapy. However, a large number of patients remain at risk for OIs because they are diagnosed at late stages of HIV disease, fail to stay in treatment, or fail to maintain viral suppression. Clinicians should remain vigilant for OIs and for changes in recommended management strategies. Issues that often arise in this regard include how to interpret polymerase chain reaction diagnostic results in individuals with HIV infection; whether primary prophylaxis for Mycobacterium avium *complex is still needed; whether clinicians should screen asymptomatic patients for cryptococcal antigen; and need for amphotericin B in treatment regimens for cryptococcal meningitis. This article summarizes a presentation by Henry Masur, MD, at the IAS–USA continuing education program held in Washington, DC, in April 2018.*

Keywords: HIV, opportunistic infections, *Pneumocystis pneumonia*, PCP, *Mycobacterium avium*, MAC, *Toxoplasma*, cryptococcal meningitis, PCR, diagnostics

Despite the success of current antiretroviral therapy (ART) in reducing the burden of HIV-related opportunistic infections (OIs), a large number of individuals living with HIV infection present late in HIV disease or do not maintain viral suppression and thus remain at risk for opportunistic diseases. Management of OIs is thus still relevant for practitioners who care for this patient population.

HIV Epidemic in Washington, DC

The current state of the HIV epidemic in Washington, DC, provides an example of the ongoing risk of OIs in current patient populations. The good news in Washington, DC, is that, thanks to the efforts of many funding agencies, federal and local health administrations, clinics and hospitals, and health care practitioners, the annual number of newly recognized cases of HIV infection in this district has been reduced from approximately 1100 to approximately 350 over the last 10 years. However, the prevalence and incidence in this district remain unacceptably high. As of 2016, the overall prevalence of HIV infection was 1.9%, including rates of 0.9% among whites, 3.1% among African Americans, and 1.2% among Hispanics/Latinos. Data from 2016 indicate that among individuals with known HIV infection, only 63% are virally suppressed, with only 47% of youth with HIV infection being virally suppressed (Figure 1). Thus, there remains a large patient population with low or declining CD4+ cell counts who are susceptible to OIs. From 2011 to 2015, 21% of newly diagnosed individuals had CD4+ cell counts below 200/µL at diagnosis; at 1 year after diagnosis, 50% of these patients still had counts below 200/µL.

Surrogate Markers for Incidence of OIs in Recent Years

In the absence of hard data on incidence of OIs in recent years, there are some indices that can provide an idea of the scope of the problem of HIV-related OIs. One such metric is how often the National Institutes of Health (NIH)-Centers for Disease Control and Prevention (CDC)-Infectious Disease Society of America (IDSA) OI guidelines are accessed online. During the period from March 1, 2017, to February 28, 2018, adult OI guidelines were accessed more than 420,000 times; of these, approximately 72,000 page views were for *Pneumocystis jiroveci* pneumonia (PCP), 45,000 for tuberculosis drug dosing, 28,000 for toxoplasmosis, and 25,000 for *Mycobacterium avium* complex (MAC).

Most-Asked Questions about OIs

Very few controlled trials related to the diagnosis, therapy, or prevention of OIs are currently being performed, in contrast to the numerous studies performed in the 1980s and 1990s. The guidelines currently rely on observational data from patients with HIV infection, and experience in other patient populations that are plausibly applicable to patients with HIV infection. Thus some of the recent changes in the guidelines are based on observational data from patients with HIV infection, and some of the recommendations are extrapolated from other patient populations.

Polymerase Chain Reaction (PCR)-Based Diagnosis

For the management of HIV-related OIs, clinicians must be aware that microbiology laboratories are changing their testing platforms dramatically. When organisms are grown in conventional media, any growth can often be identified by genus and species within a few hours by techniques such as Matrix Assisted Laser Desorption/Ionization/Time of Flight Mass Spectrometry (MALDI-TOF) Other specimens are tested by qualitative nucleic acid amplification methods that are extremely sensitive for minute quantities of organisms and are highly specific for identifying organisms accurately. Thus, the clinician is getting information faster, and can obtain

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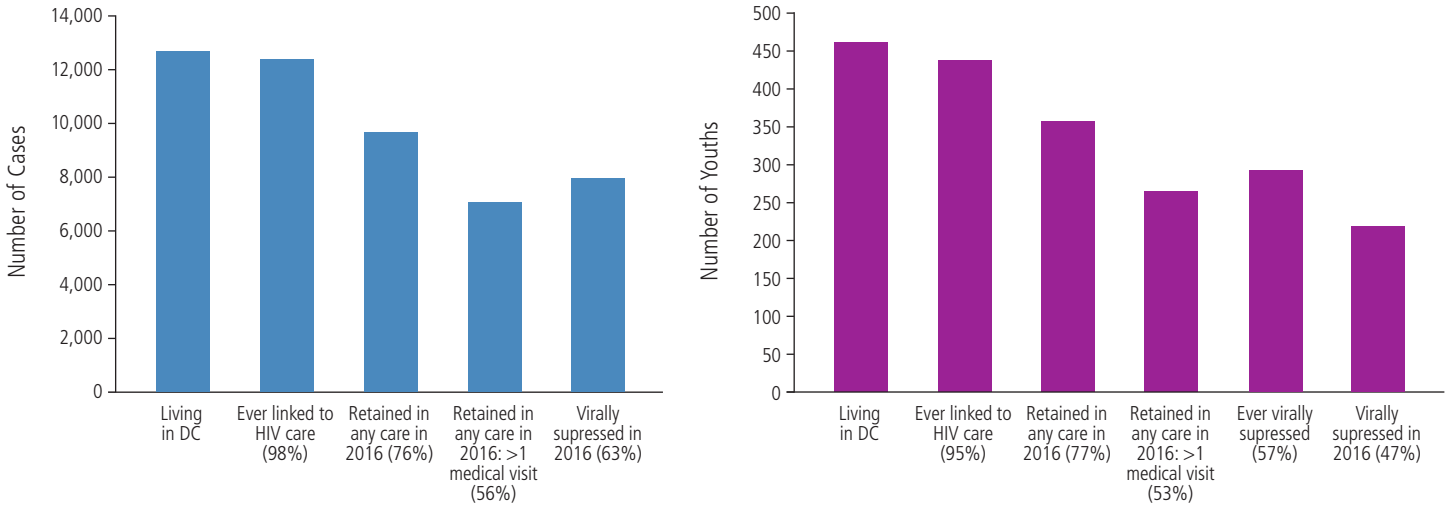

Figure 1. Contact with HIV care and viral suppression among known individuals (left) and youth (right) with HIV infection in Washington, DC (DC) in 2016. Adapted from the DC Health Annual Epidemiology and Surveillance Report, 2017.[10]

far more sensitive testing, often with concurrent information about whether specific resistance-associated genes are present. Thus, the data coming to clinicians must be interpreted with analytic approaches that are considerably different from interpretations that clinicians made when diagnoses were established based on smears of biologic fluids and tissues, conventional cultures, antigen detection assays, and serum antibody tests. For example, increasingly, laboratories are not performing immunofluorescence assays for PCP, with diagnoses being primarily based on PCR assays.

The question is whether the detection of an organism in respiratory sample, stool, cerebrospinal fluid (CSF), or blood is an indication that the identified organism is causing the syndrome of concern rather than being detected as a bystander/colonizer or contaminant. For instance, when bronchoalveolar lavage fluid is tested by the Biofire Platform (Salt Lake City, Utah), does the detection of an organism provide the clinician with assurance that *Pneumocystis* is the causative organism?

Consider a scenario in which a 35-year-old patient recently diagnosed with HIV infection has a nadir CD4+ cell count of 90/μL and is on dolutegravir-based ART, and presents with low-grade fever and cough. For the Biofire 2 panel, the appropriate specimen to detect upper respiratory pathogens is a nasopharyngeal swab (not nasal swab) so that cells in the posterior retropharynx are collected. The Biofire upper respiratory panel tests for a number of bacteria such as *Bordetella*, *Chlamydophila pneumonia*, and *Mycoplasma pneumonia*, and several viruses such as influenza, parainfluenza, coronavirus and adenovirus. If the specimen is positive for coronavirus, for example, how much confidence is there that the identified agent is the cause of the patient's syndrome?

Coronavirus may be present in very small quantities and represent colonization following an acute infection days or weeks before, depending on the patient's immune status (ie, some immunosuppressed persons can shed a respiratory virus for many months after an acute infection). If coronavirus is the only pathogen detected, the clinician might assume that coronavirus has caused the clinical illness, assuming the clinical illness is compatible with what is known about a coronavirus infection. However, the patient may in fact be infected with an organism not tested for by this platform, or missed by this specimen or by a process that is not due to an infection.

For lower respiratory panels, there are similar difficulties with interpreta tion of these sensitive detection systems. Patients may have colonization in their lower respiratory tracts (or in upper respiratory secretions contaminate lower respiratory specimens) with respiratory viruses, or with MAC, *Cryptococcus*, or *Pneumocystis*. Thus, because PCR is ultrasensitive compared with conventional smears and cultures, a negative PCR test is convincing evidence that the pathogen is not present. A positive result, however, must be evaluated in the context of the clinical situation, and what other pathogens or processes are concurrently present. Some pathogens that can colonize the airways of an individual with HIV infection, including herpes simplex virus, cytomegalovirus (CMV), MAC, and *Candida*, are so rarely the cause of pulmonary dysfunction in persons with HIV infection, even those with very low CD4+ cell counts, that they should be considered as extremely unlikely etiologic agents for pulmonary dysfunction.

Conventional cultures can detect colonizers as well, but conventional cultures are not as sensitive as PCR. Thus, when the cultures are positive, the quantity of organisms present is more likely to indicate causality; the same is true for a smear. In addition, in contrast to PCR, conventional cultures can be quantitative or semiquantitative, and can be interpreted in association with smears.

As an example of the diagnostic uncertainty associated with multiplex results, consider a patient who looks toxic, has diffuse bilateral infiltrates, and has an oxygen saturation level of

91% on room air. A pulmonologist performs bronchoalveolar lavage and a lower respiratory tract PCR panel is ordered. If the result comes back as positive for *Pneumocystis*, CMV, *Cryptococcus*, *Toxoplasma*, or coronavirus, which would be convincing as the cause of the patient's pulmonary pathology? Although any of these organisms could be the cause of the pulmonary dysfunction, the most suggestive finding would be *Toxoplasma*, because it is the only organism among these that is not ordinarily found in the respiratory tract as a latent organism. CMV and coronavirus are rarely the cause of serious lower respiratory tract infection in individuals with HIV infection. *Cryptococcus* is not common, but would be a consideration. *Pneumocystis*, as mentioned above, could be the cause of the pulmonary dysfunction or could be colonizing the respiratory tract.

Thus, as we evolve into the era of PCR diagnostics, guidelines are struggling with how to make a diagnosis for *Pneumocystis* if the laboratory does not perform immunofluorescence. Similar considerations apply to the detection of other bacteria, viruses, fungi, and protozoa in these multiplex panels. Clinicians need to be cognizant of what tests the laboratory is performing when they interpret report the presence of organisms in a biologic specimen.

Multiplex PCR platforms are currently being used by many diagnostic laboratories for stool, CSF, and blood. Some platforms also detect the presence of resistance-associated genes for certain pathogens, such as *mecA* and *mecC* for methicillin-resistant *Staphylococcus aureus*. As with respiratory specimens, the issue for clinicians will be how to determine if the presence of a pathogen qualitatively (with no quantitation) is convincing evidence of the need to treat the organisms identified.

MAC Prophylaxis

The use of chemoprophylaxis for the prevention of OIs is still an important component of HIV care. However, patients will rarely take OI prophylaxis without also taking ART. For patients who respond to ART, once the viral load falls below the level of laboratory detection, the degree of immunoincompetence is diminished substantially, even if the CD4+ cell count has not risen substantially. However, determining when OI prophylaxis can be stopped has been difficult if one is using viral load and CD4+ cell count as interacting factors.

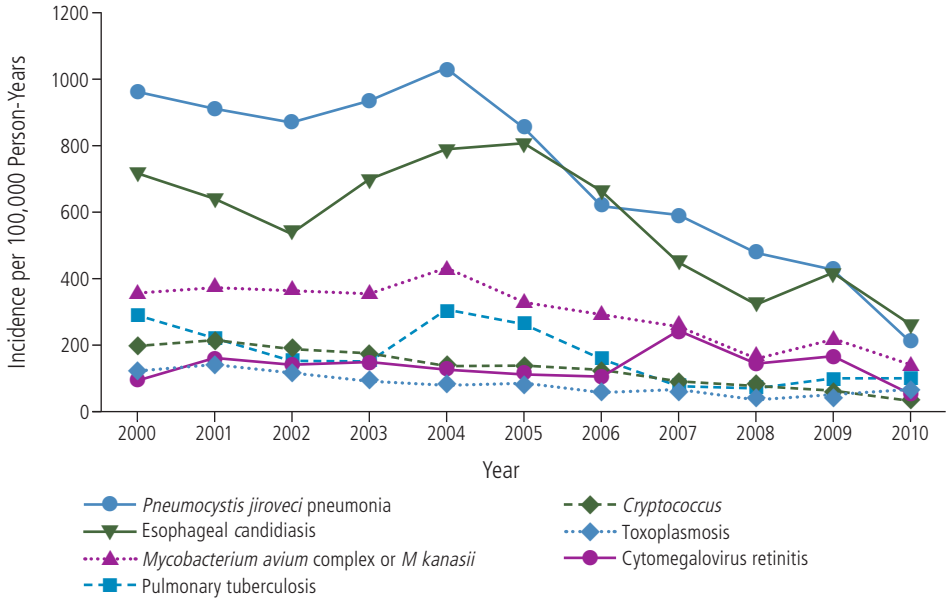

Figure 2. NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) data on incidence of HIV-related opportunistic infections in 2000 to 2010 in the United States and Canada (n=63,541). Adapted from Buchacz et al.[4]

Guidelines and most experts still advocate using CD4+ cell count criteria for stopping and starting OI prophylaxis. OI prophylaxis is especially important for patients with low CD4+ cell counts who take their medications regularly, but who have drug-resistant virus and thus low CD4+ cell counts and high viral loads.

There have been few changes in recommendations for prophylaxis except for the recommendations for MAC. The current IAS-USA guidelines[1,2] do not recommend primary MAC prophylaxis for individuals on effective ART, and the NIH-CDC-IDSA guidelines[3] do currently, as of August 2018, recommend such prophylaxis. The latter guidelines are likely to change in the very near future on the basis of accumulating observational evidence about the rare occurrence of MAC in the current era. As shown in Figure 2, data through 2010 show the decline in OIs during the potent combination ART era. Although not exhibiting as great a decline as PCP, the incidence of MAC was reduced by approximately 45% between 2000 and 2010.[4]

Data from HOPS (HIV Outpatient Study) suggests that the risk of MAC is low among patients on ART who have nadir CD4+ cell counts below 50/μL, even in the absence of primary prophylaxis.[5] Of special interest, among patients in the study with CD4+ cell counts below this threshold who were started on ART, there were no cases of MAC among 41 who did not receive prophylaxis nor among 30 who did. This is a small sample size, but it illustrates the dearth of cases in most observational studies.

The uncommon individuals with HIV infection who do develop disseminated MAC today have much better survival than they would have 1 or 2 decades ago, which is not unexpected given the efficacy of current ART. Data from San Francisco show declining mortality from AIDS-defining OIs, including MAC, with the advent of potent combination ART, with many patients having long-term survival after MAC diagnosis (Figure 3).[6] Based on the facts that there is a lower incidence of MAC in this country, that those who start ART

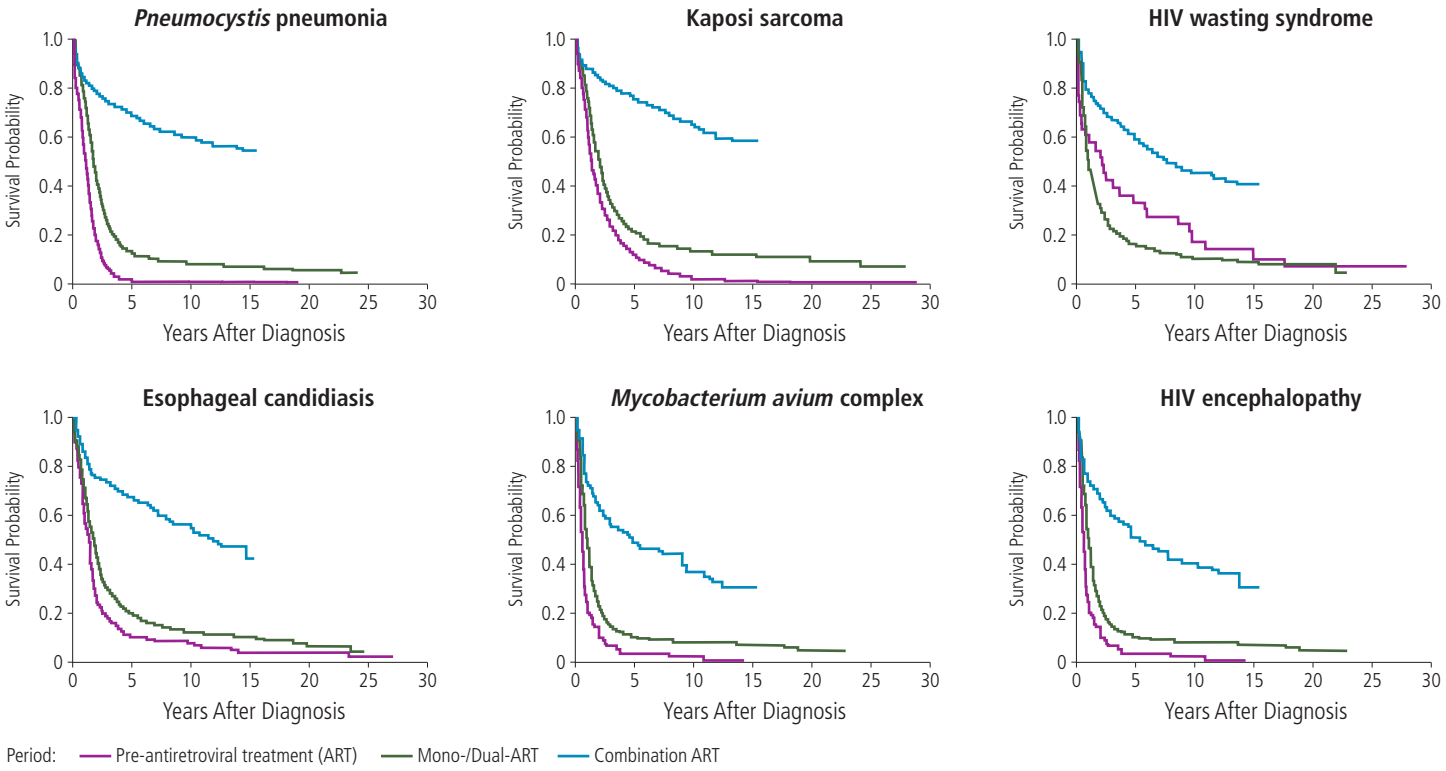

Figure 3. Survival after diagnosis of selected AIDS-defining opportunistic infections in San Francisco, California, 1981 to 2012 (n=20,858). Adapted from Djawe et al.[6]

appear to have low risk of MAC disease whether on prophylaxis or not, and that we are managing the disease better, the NIH, CDC, and IDSA will likely also soon recommend that no primary MAC prophylaxis is needed if effective ART is initiated and viral suppression is achieved.

It is also important to note that the incidence of disseminated MAC in this era can be confounded by cases of immune reconstitution syndrome (IRIS) that are associated with lymph node or other culture-positive tissue, ie, some definitions of disseminated MAC may include positive blood cultures for MAC. Incidence and mortality data need to be carefully assessed to determine what patient population is being described, ie, only those with positive blood cultures, or those with positive cultures only from sites other than blood who may have IRIS.

Screening for Cryptococcal Antigen at CD4+ Cell Counts Below 100/µL

The World Health Organization recommends screening for cryptococcal antigen in patients with CD4+ cell counts below 100/µL, whereas NIH-CDC-IDSA guidelines leave screening to the discretion of practitioners. Most practitioners in the United States do not perform such screening. The practice of US practitioners likely reflects the finding that in the United States, the frequency of asymptomatic cryptococcal antigenemia is low: approximately 2.9% of asymptomatic patients with a CD4+ cell count below 100/µL and 4.6% with CD4+ cell counts below 50/µL have a positive cryptococcal antigen test. The range of antigen titers observed in these cases spans from very low to impressively high. Some patients do develop a syndrome following initiation of ART that may be related to *Cryptococcus*, but it is also hard to determine whether this disease is related to active organism replication, or if it is IRIS.

If screening for asymptomatic cryptococcal antigen is done, and a positive result is obtained, a lumbar puncture should be performed to determine if the patient has asymptomatic meningeal infection. If the patient has a negative CSF cryptococcal antigen test, some clinicians would choose to treat with ART alone. Others would treat with ART plus fluconazole. If the CSF antigen is positive, liposomal amphotericin B plus flucytosine is the regimen of choice.

Thus there remains uncertainty regarding screening in the United States. Potential advantages of screening include the fact that earlier cryptococcal meningitis treatment leads to better outcomes and that risk of IRIS is reduced by treating cryptococcal disease for 2 to 8 weeks before starting ART. To date, there is very little evidence in the United States that survival among asymptomatic patients is better with prospective monitoring than with a strategy that initiates treatment when patients have manifestations due to active cryptococcal disease. These manifestations might include fever, headache, or more obvious presentations of meningitis, sepsis, or other organ involvement.

Does Amphotericin B Need to be Used in Cryptococcal Meningitis?

Another frequently asked question regarding cryptococcal disease is

whether there are recommended regimens for cryptococcal meningitis that do not include liposomal amphotericin B. Azole drugs are fungistatic, whereas amphotericin B is fungicidal. It has been demonstrated that there is a good correlation between outcome of disease and reduction in CSF cryptococcal titers. A number of studies have examined whether higher doses of azoles can be as effective as amphotericin B. A study reported at the 2018 Conference on Retroviruses and Opportunistic Infections showed that increasing fluconazole doses as high as 2000 mg/day did not provide the same CSF clearance rate as amphotericin B. The proportions of patients with negative CSF cultures at week 10 were 45%, 56%, and 60% with fluconazole doses of 1200, 1600, and 2000 mg/day, respectively, compared with 81% with amphotericin B treatment.[7]

Thus, in the United States, it continues to be recommended that an amphotericin-based regimen be used in all cases of cryptococcal meningitis (fluconazole alone can be used for nonmeningeal disease). Liposomal amphotericin plus flucytosine is the most rapidly fungicidal regimen. Amphotericin B plus fluconazole is also recommended as an alternative regimen, exhibiting similar mortality rate but slower CSF sterilization.

There is also debate about whether corticosteroid therapy should be used empirically when starting therapy for cryptococcal meningitis. One study has shown a higher rate of poor outcomes and adverse events when dexamethasone was added to amphotericin B plus fluconazole. Thus, empiric corticosteroids in the absence of evidence of increased intracranial pressure are not recommended.

Which Varicella Zoster Virus Vaccine Is Recommended

Another frequently asked question is whether a recently developed varicella zoster virus vaccine should be used in individuals with HIV infection. The previous live attenuated vaccine is contraindicated in patients with CD4+ cell counts below 200/µL. It is recommended for patients with CD4+ cell counts over 200/uL, although their immunologic response is not as robust as individuals without HIV infection.

A newer recombinant adjuvant vaccine has become available—a 2-dose subunit vaccine containing recombinant glycoprotein E in combination with a novel adjuvant. It is 68% effective for reducing the occurrence of clinical varicella zoster virus infection in post-hematopoietic stem cell transplant recipients. However, there are very limited data in HIV infection, with 2 small studies having assessed safety and immunologic response, but not clinical efficacy. Whether this vaccine will become the recommended immunization for individuals with HIV infection with CD4+ cell counts below or above 200/uL is unknown. The use of this vaccine seems plausible because it is not a live virus vaccine. However, the effect of the adjuvant has not been studied in this population, nor has the clinical efficacy been established.

Similarly, there are no robust efficacy data for the new adjuvanted hepatitis B vaccine, nor are there extensive safety data in the population with HIV infection for this adjuvanted product. Thus, at this time this new vaccine is not recommended for populations with HIV infection, although there is no evidence at this time that the vaccine is harmful or less effective than the current product.

Treatment for *Toxoplasma* Encephalitis

A common question regarding treatment for *Toxoplasma* encephalitis is: If pyrimethamine is either unavailable from suppliers or too costly for insurance plans, is trimethoprim-sulfamethoxazole (TMP-SMX) an appropriate initial therapy. And: Is TMP-SMX superior to atovaquone?

Data from an observational trial reported in 2009 showed good results with TMP-SMX that appeared based on small numbers of cases to be comparable with those reported for pyrimethamine.[8] Clinical response was observed overall in 77 (93%) of 83 patients, including response in 26 of 28 patients who were retreated for second episodes. Treatment-limiting toxicity of TMP-SMX was observed in 6 patients (7%). A small comparative trial reported in 1998 showed no difference in progression rates between 35 patients receiving pyrimethamine-sulfadiazine (14%) and 37 receiving TMP-SMX (16%).[9]

The regimens of choice for toxoplasmosis based on extent and quality of evidence remain pyrimethamine plus sulfadiazine (plus leucovorin) or pyrimethamine plus clindamycin (plus leucovorin). If pyrimethamine is not available, TMP-SMX is the highest-rated alternative. TMP-SMX has the additional advantage that it can be given intravenously, an advantage for seriously ill patients. Pyrimethamine cannot be administered parenterally.

Atovaquone is not quite as reliable as sulfadiazine-pyrimethamine, because the time to steady state levels is 3 to 4 days and absorption can be erratic if the patient is not taking a high-fat diet. Atovaquone with or without another drug is adequate but not considered to be as effective as TMP-SMX.

Is Hepatitis A an OI?

An outbreak of hepatitis A infection began in San Diego County in California in November 2016 and spread to Santa Cruz, Los Angeles, and Monterey Counties, and now to several other states. On this basis, there have been many questions regarding whether hepatitis A is an HIV-related OI. There was a report of 704 cases of hepatitis A virus infection in this outbreak, with 461 hospitalizations and 21 deaths. Although some cases occurred in patients with HIV infection, the epidemiologic association with acquisition was poor sanitation in the context of homelessness and among individuals who use injection drugs. Presence of hepatitis B virus and hepatitis C virus, but not HIV infection, were correlated with morbidity and mortality. Thus, hepatitis A is not considered an HIV-associated OI and is unlikely to be featured in OI guidelines. However, hepatitis A immunization should be offered to all individuals with HIV infection who are seronegative for antibody to hepatitis A virus.

Conclusion

OIs remain a major challenge for individuals with HIV infection. A substantial number of people in the United States continue to present with 1 or more OIs as the initial manifestation of their HIV infection. A substantial number of individuals with HIV infection are not in continuous care and do not have durable viral suppression.

Although new antifungal and antiherpes virus drugs and new immunizations are becoming available, few of them have been assessed in populations with HIV infection in robust controlled trials. Thus, updates of guidelines for management of OIs in individuals with HIV infection in terms of prevention or therapy will have to rely on observational studies of individuals with HIV infection and plausible inferences from other populations.

Presented by Dr Masur in April 2018. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Masur in September 2018.

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