Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Updated Guidelines From the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America

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In May 2013, a revised and updated version of the Centers for Disease Control and Prevention/National Institutes of Health/HIV Medicine Association Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents was released online. These guidelines, since their inception in 1989, have been widely accessed in the United States and abroad. These guidelines have focused on the management of HIV/AIDS-related opportunistic infections that occur in the United States. In other parts of the world, the spectrum of complications may be different and the resources available for diagnosis and management may not be identical to those in the United States. The sections that have been most extensively updated are those on immune reconstitution inflammatory syndrome, tuberculosis, hepatitis B, hepatitis C, human papillomavirus, and immunizations. The guidelines will not be published in hard copy form. This document will be revised as needed throughout each year as new data become available.

Keywords. opportunistic infections; HIV/AIDS; guideline; revision; online.

The 2013 revision of the Centers for Disease Control and Prevention/National Institutes of Health/HIV Medicine Association Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0) reflects work by the Adult and Adolescents Opportunistic Infections Working Group of the Office of AIDS Research Advisory Council, National Institutes of Health, a panel of experts from academia, professional societies, clinical practice, and US government agencies. Since the guidelines' inception in 1989 [1–7], the goal has been to provide practitioners in the United States with current, practical, evidence-based recommendations for the management of human immunodeficiency virus (HIV)/AIDS-related opportunistic infections (OIs) based on review of the literature and advice of subject matter experts. The document addresses the prevention and treatment of HIV-related OIs that are likely to be seen in the United States, acknowledging that other countries may have unique epidemiologic profiles and diagnostic and therapeutic capacities that would alter the optimal approach

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to management of OIs in those areas. These guidelines supplement companion federal HIV guidelines on antiretroviral therapy (ART) for adults and adolescents, ART for children, ART use for maternal health and prevention of perinatal transmission, management of OIs in pediatric patients, and other issues vital to comprehensive management of HIV infection, HIV-related disorders, and HIV exposures (www.aidsinfo.nih.gov/guidelines).

There are many operating procedures for developing guidelines. For the past 24 years, these guidelines on HIV-related OIs have been developed by subject matter experts and patient representatives chosen by the sponsoring organizations. Each expert is required to disclose all potential financial conflicts of interest, and these conflicts are then managed according to the sponsoring organization guidelines. The recommendations are based on thorough review of pertinent literature by committee members, and teleconference or live meetings to discuss the credibility of the data, the strength of evidence, and the wording of the document. The guidelines are edited and approved by the coeditors, who are appointed by the sponsors and who are free of conflicts. The guidelines are read by generalists and patient representatives for content, feasibility, and readability. The quality of supporting data and the strength of the recommendations are graded.

Comments from readers regarding the document are considered by the coeditors. Such comments can be directed to contactus@aidsinfo.nih.gov.

With this edition, these guidelines will be an online only document [8]. This format will allow for more timely and more frequent updates of the guidelines in an era when practitioners and patients expect guidelines to promptly reflect clinical advances. The guidelines subject matter experts will keep abreast of newly published information and literature that may provide evidence or indications to support revision of the recommendations in their section. When such situations arise, the committee will convene a meeting to review the data and make suggested revisions. Since the release on 7 May 2013, as an example, the guidelines have already been updated in response to the discontinuation of the manufacture of the ganciclovir ocular implant. This update is clearly indicated on the guideline website in a section labeled "What's New in the Guidelines" (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0), dated 8 July 2013. The page will have a date indicating when the guidelines were last reviewed and a date indicating when the guidelines were last updated.

The coeditors will convene a quarterly meeting of the subject matter leads to assure that the literature is being reviewed and that changes, when necessary, are expeditiously incorporated. These guidelines will continue to include information that has been thoroughly reviewed, and thus, will rely primarily on published, peer-reviewed data, utilizing abstracts or other sources only when such information can be thoroughly reviewed and is judged to be compelling. The coeditors are in regular communication with leadership of other federal and professional society guideline committees to maximize the likelihood that recommendations among different documents can be harmonized.

Numerous studies have documented the dramatic decline in the incidence of HIV-related OIs among cohorts of patients with reliable access to effective ART [9–13]. By suppressing plasma HIV RNA levels and by increasing CD4 cell counts, ART reduces the risk of developing HIV-associated OIs and malignancies [14].

Why, then, are these guidelines still relevant in the United States in 2013 when potent well-tolerated ART can now provide near-normal survival that is generally free of the OIs that were so devastating and prevalent in the 1980s and 1990s [15]?

The leading reason why these guidelines remain relevant is that many HIV-infected persons in the United States have not achieved optimal suppression of HIV replication. More than half of all HIV-infected persons in the United States live in 12 urban areas where access to care is especially uneven [16–19]. Extensive studies of the various steps in the "HIV treatment cascade"—from diagnosis of infection to suppression of plasma HIV RNA—have documented that in the United States, both as a whole and regionally, <25% of HIV-infected individuals are aware they are infected, linked and retained in continuous care, prescribed effective ART and OI prophylaxis (when indicated), and virologically suppressed [13, 14, 16–21]. The reasons for this stunning gap are numerous. General themes include economic disenfranchisement, geographic barriers, lack of awareness and of risk, stigma, and lethargy regarding a disease now often portrayed and perceived as treatable and not life-threatening. Despite substantial public health research and action, too many patients continue to first present to medical care during the very advanced stages of HIV disease with OIs and HIV-related malignancies when the severity of these preventable illnesses forces them to seek medical attention, often at hospital emergency rooms and primary care facilities with limited HIV expertise.

Patients continue to present with OIs and HIV-related malignancies in 2 other important contexts, in addition to these being seen as the initial clinical indicator of HIV infection. First, it is not uncommon for patients who initiate ART at low CD4 cell counts to have an OI "unmasked" [22]. In the United States, typical OIs that emerge in this context include disseminated *Mycobacterium avium* complex disease, tuberculosis, cytomegalovirus retinitis, *Pneumocystis* pneumonia, and Kaposi sarcoma [23]. Second, some patients initiating ART at low CD4 cell counts can manifest a paradoxical worsening of an OI after ART is initiated [24–26]. These 2 phenomena, which comprise the immune reconstitution inflammatory syndrome (IRIS), complicate

clinical management and can cause considerable morbidity, and occasionally mortality. Clinicians must be knowledgeable about the detection and management of these syndromes. For some OIs, diagnostic and therapeutic considerations related to IRIS can be especially vexing. Information regarding management of IRIS for some OIs are detailed in these guidelines.

In addition, although patients who have durably suppressed HIV replication for many months or years benefit from remarkable reduction in the occurrence of OIs and AIDS-defining malignancies, improved immunity does not ameliorate all risk of incident OIs [11], even at CD4 cell counts >200 cells/μL. There are well-documented reports where risk of some infections remains even at higher CD4 counts, especially for tuberculosis, herpes zoster, pneumococcal disease, and Kaposi sarcoma [27–31]. Thus, although long-term, effective virologic suppression reduces the risk of HIV-related infectious complications in these patients, it does not completely eliminate it. Healthcare providers need to be knowledgeable about recognizing and managing OIs and to consider their diagnosis as a late presentation of HIV infection, as IRIS, and as illness in persons with high CD4 cell counts.

Finally, as HIV-infected patients are living longer, clinical disorders are emerging that were not major HIV-related complications when life expectancy after HIV diagnosis was shorter. These diseases include chronic liver disease and hepatoma due to hepatitis B and C virus infection, as well as cervical, anal, and oral carcinomas related to human papillomavirus (HPV) infection, and accelerated atherosclerotic and cerebrovascular disease [32–35]. These processes require active, prospective management to minimize their impact on patients with durably suppressed HIV replication.

What is new in these guidelines, since their last publication in 2009? Considerable data have been published about the diagnosis and management of IRIS, especially as this syndrome relates to tuberculosis and cryptococcosis [20, 21]. New guidance is provided by this document for managing IRIS related to some OIs, where data are available. Sections on the management of ART in the context of tuberculosis and on hepatitis B and hepatitis C virus infection have been updated. The treatment of hepatitis C infection is evolving rapidly and updates online can be expected as new agents are approved and data on their efficacies in HIV-infected patients become available. For the first time in decades, new drugs for tuberculosis are being developed, and updates can also be expected as these agents are approved and data on how best to use them in the context of ART emerge. Immunization strategies for preventing pneumococcal disease and HPV infection have been updated to reflect the availability of new vaccine products and new data. Information about drug interactions has been updated, especially as the information relates to antiretroviral agents approved since the last guidelines update.

The guidelines contain tables at the end of each chapter and summary tables at the end of the document that list therapeutic options for preventing and treating OIs, adverse drug events, drug–drug interactions, dosing in patients with renal insufficiency, and therapeutic considerations during pregnancy. These tables complement narrative sections in each chapter on clinical manifestations, diagnosis, and prevention and treatment of each OI.

Thus, in 2014, up-to-date, authoritative information on the management of HIV-related OIs is still relevant to patients who develop OIs because of late diagnosis of HIV, poor access to HIV care, or ineffective HIV or preventive therapy. One can hope that, in the years to come, whereas this information will be useful, fewer and fewer patients will require treatment for OIs as prevention strategies become more effective and as patients are diagnosed soon after acquisition of HIV, are linked to continuous care, and receive effective ART.

Notes

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