

Review

What's New in the 2009 US Guidelines for Prevention and Treatment of Opportunistic Infections Among Adults and Adolescents With HIV?

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Despite dramatic declines in the incidence of opportunistic infections (OIs) in the United States, they remain an important cause of morbidity and mortality for HIV-infected persons. Previously separate guidelines on the prevention of OIs and on the treatment of OIs have been combined recently into an updated single document; the present article reviews salient changes to and new information contained in this guidance. Chapters on hepatitis B virus infection and tuberculosis have been expanded substantially, and each chapter now includes information on immune reconstitution inflammatory syndrome. In addition, there is detailed discussion on the role of antiretroviral therapy in OI prevention and issues concerning the initiation of antiretroviral therapy during treatment of an acute OI. In the future, these guidelines will likely be maintained as an internet-based document to facilitate wider dissemination and more rapid updates.

This year, guidelines for the prevention and treatment of opportunistic infections (OIs) in HIV-infected adults and adolescents were updated.¹ Published as part of the *Morbidity and Mortality Weekly Report's Recommendations and Reports* series, these guidelines embody the contributions of more than 140 content matter experts collaboratively edited by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA). The 2009 report updates and combines earlier versions of separate guidelines: recommendations for the prevention of OIs last published in 2002² and recommendations for the treatment of OIs first published in 2004.³ The 2009 document can be downloaded at <http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf>. Here, we highlight and discuss some of the important changes that have been made to the guidelines since their last update. A parallel set of pediatric guidelines will be published later in 2009.

These guidelines are intended for use by clinicians in the United States. In other regions of the world, especially sub-Saharan Africa and southeast Asia, the spectrum of OIs differs and the di-

agnostic testing (including radiologic imaging), antimicrobial therapy, and vaccines available are typically more limited. Different guidelines for prevention and treatment of OIs might be appropriate for these regions.

With advances in antiretroviral therapy and OI prophylaxis, the incidence of OIs in the United States and many other resource-rich nations has fallen dramatically (see Figure 1).⁴ Although there has been an increase in morbidity and mortality from what are often termed non-AIDS-defining conditions in the United States, OIs remain a leading cause of hospitalization and death for persons with HIV infection.⁵⁻⁹ Persistent health disparities in the United States exacerbate the disproportionate number of

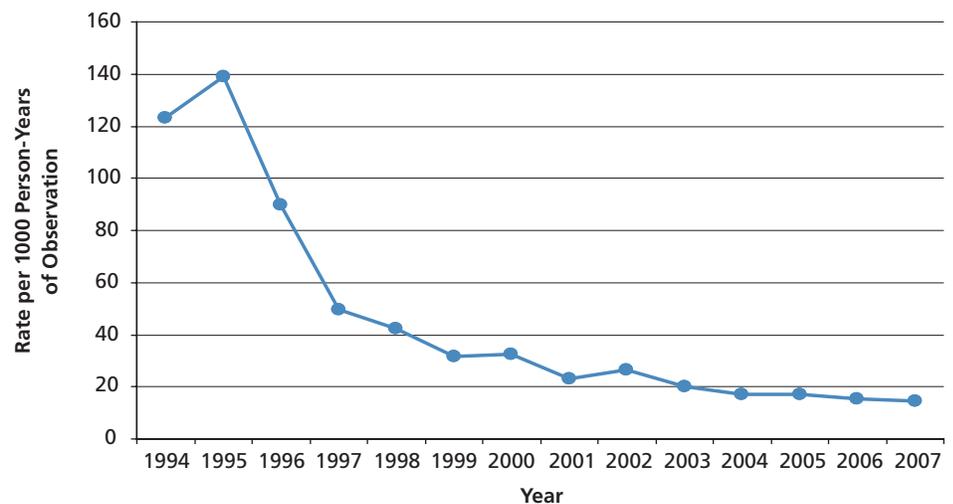


Figure 1. Annual incidence of first AIDS-defining opportunistic infection in the HIV Outpatient Study, 1994–2007. Figure adapted from Brooks et al, *Clin Infect Dis*, 2009.⁴

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Table 1. Organization of Information by Chapter Subsections in the Guidelines

Epidemiology
Clinical Manifestations
Diagnosis
Preventing Exposure
Preventing Disease
– Initiating Primary Prophylaxis
– Discontinuing Primary Prophylaxis
Treatment of Disease
Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome
Management of Treatment Failure
Preventing Recurrence
Discontinuing Secondary Prophylaxis (Chronic Maintenance Therapy)
Special Considerations During Pregnancy

Adapted from Kaplan et al, *Morb Mortal Wkly Rep*, 2009.

patients with acute OIs presenting to urban and public health care facilities. As the number of persons living with HIV infection in the United States continues to increase and the existing clinical work force ages and retires, we must ensure that practitioners remain competent in the management of HIV-associated OIs.

Organization of the Guidelines

The update includes sections on 29 OIs, with each section organized according to the same series of subsections (Table 1). As in previous editions of the guidelines, prevention and treatment recommendations are rated by a system that includes a letter (A through E) to indicate the strength of the recommendation and a Roman numeral (I through III) to indicate the quality of the evidence supporting the recommendation (Table 2). The guidelines now contain 11 tables, 2 figures, and an appendix with recommendations for lowering the risk of acquiring OIs associated with a variety of specific exposures (eg, sexual or pet-related exposures).

Definition and Selection of Opportunistic Infections for Inclusion

In 1995, authors from the CDC, NIH, and IDSA defined OIs as “infections that cause disease with increased frequency and/or of increased severity among HIV-infected persons, presumably because of immunosuppression.”¹⁰ That publication included more than 100 infections satisfying this definition. The OIs most predictive of severe HIV infection define AIDS, and those OIs are included among the AIDS-defining conditions in the CDC AIDS case definition.¹¹

The OIs included in the 2009 guidelines encompass all AIDS-defining infections and other infections that (1) are more prevalent among HIV-infected persons residing in the United States, (2) cause more severe clinical illness among HIV-infected persons, (3) are uniquely related to noninfectious AIDS-defining conditions, or (4) have aspects of prevention or treatment that are

unique to HIV-infected persons. In addition to the CDC AIDS-defining OIs, these OIs include bartonellosis, syphilis, aspergillosis, human herpesvirus-6, -7, and -8 infections, human papillomavirus infection, and hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. The guidelines also include recommendations on 5 “geographic” OIs—diseases that are endemic outside the United States but might be acquired by HIV-infected persons as a result of foreign travel, or diseases that may be seen in the United States among immigrant populations (see below).

Chemotherapy for Prevention and Treatment of Acute Opportunistic Infections

The guidelines provide small refinements to prior editions regarding the management of major OIs such as *Pneumocystis pneumonia* (PCP), toxoplasmosis, cytomegalovirus (CMV) infections, disseminated *Mycobacterium avium* complex (MAC) infection, and

Table 2. System Used to Rate the Strength of Recommendations and Quality of Supporting Evidence

Rating Strength of Recommendation	
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B	Moderate evidence for efficacy—or strong evidence for efficacy but only limited clinical benefit—supports recommendation for use. Should generally be offered.
C	Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (eg, drug toxicity, drug interactions) or cost of the treatment or alternative approaches. Optional.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.
Rating Quality of the Evidence Supporting the Recommendation	
I	Evidence from at least 1 properly designed randomized, controlled trial.
II	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Adapted from Kaplan et al, *Morb Mortal Wkly Rep*, 2009.

cryptococcosis. For each OI included in this revision of the guidelines, Table 1 of the guidelines summarizes primary prevention recommendations, and Table 2 of the guidelines summarizes preferred and alternate treatment recommendations.

The Role of Antiretroviral Therapy for Preventing Opportunistic Infections

Effective antiretroviral therapy remains the mainstay for preventing OIs. Increasing the CD4+ cell count (CD4+ count) and reducing plasma HIV RNA level, regardless of pretreatment CD4+ count, each reduce the risk of acquiring OIs. The introduction to the guidelines emphasizes the importance of identifying HIV-infected persons before their CD4+ counts fall to levels that increase their susceptibility to OIs.

When to Start Antiretroviral Therapy in Patients With Acute Opportunistic Infections

Initiating antiretroviral therapy during an acute OI poses a variety of dilemmas. It can complicate the clinical scenario by introducing antiretroviral therapy–related drug toxicities and drug-drug interactions between antiretroviral drugs and antimicrobial therapy for the OI. Alterations in renal and hepatic function related to the acute OI can distort antiretroviral therapy pharmacokinetics (eg, metabolic clearance, volumes of distribution) and reduce antiretroviral efficacy or increase antiretroviral toxicity. Acute gastrointestinal OIs can decrease antiretroviral drug absorption, producing serum levels that only partially suppress HIV RNA level and thereby generate selection pressure favoring emergence of antiretroviral drug resistance.

Antiretroviral therapy–mediated immune reconstitution, which is the goal of antiretroviral treatment, can also substantially complicate acute OI treatment by augmenting inflammatory responses that intensify end-organ injury. This immune reconstitution inflammatory syndrome (IRIS) has now been reported in association with a wide va-

riety of OIs, although it has been best characterized for tuberculosis, disseminated MAC infection, PCP, cryptococcosis, and CMV retinitis.

In addition to managing the acute OI and the patient's HIV infection, IRIS can be a third condition the clinician must address. The term IRIS describes both the paradoxical worsening of an existing OI after initiating antiretroviral therapy as well as the unmasking of OIs that were clinically latent or subclinical and unrecognized before initiation of antiretroviral therapy. IRIS typically occurs within 4 weeks to 8 weeks of starting antiretroviral therapy. Risk of IRIS is highest among persons who experience rapid increases in CD4+ counts, especially if initiating therapy at very low CD4+ counts (ie, < 100 cells/ μ L) with high plasma HIV RNA levels. IRIS can be very difficult to distinguish from active, acute infections and can manifest at sites other than the anatomic location where the OI was first diagnosed. Treatment of IRIS ranges from "watchful waiting" to therapy with nonsteroidal or steroidal antiinflammatory drugs and can include change in or intensification of the OI antimicrobial regimen. Each section in the guidelines now includes information on whether IRIS has been described in association with the particular OI.

Initiating antiretroviral therapy during treatment for an acute OI requires careful consideration and close clinical monitoring. For some OIs for which no specific therapy has been shown to be effective, such as cryptosporidiosis, certain microsporidiosis, progressive multifocal leukoencephalopathy (PML), and some infections caused by highly drug-resistant pathogens (eg, multiresistant herpes simplex virus), immediate initiation of antiretroviral therapy is warranted, even though IRIS can occur and would worsen the patient's clinical condition (eg, PML). However, for OIs for which directed therapy is available, should antiretroviral therapy be deferred until the OI has been substantially treated? Results of a recently completed clinical trial referenced in the guidelines as an abstract have since been published¹² and suggest the answer is no.

This study examined survival among patients with acute OIs randomly assigned to early antiretroviral therapy (initiated within 16 days of starting acute OI treatment) versus deferred antiretroviral therapy (6-12 weeks later). The findings demonstrated that in the absence of major contraindications, antiretroviral therapy should be initiated early in patients with an acute OI. Notably, this study of predominately North American patients excluded persons with tuberculosis, which remains a low-incidence OI in the United States. However, a recently completed randomized, controlled clinical trial from South Africa has suggested that initiating antiretroviral therapy during antituberculosis treatment is also superior to deferral.¹³ The recommendations in the guidelines regarding initiation of antiretroviral therapy in patients with an acute OI are summarized in Table 3.

Management of Antiretroviral Therapy in Patients With Opportunistic Infections

As noted above, OIs that occur within the initial 12 weeks of antiretroviral therapy are typically attributed to latent or incubating infections unmasked when antiretroviral therapy was started (ie, IRIS). OIs presenting during this phase of antiretroviral therapy do not represent antiretroviral failure, and both the OI antimicrobial regimen and the antiretroviral therapy should be continued. OIs that occur after 12 weeks to 24 weeks of antiretroviral therapy in patients who have demonstrated an initial response to therapy (ie, increased CD4+ count, decreased plasma HIV RNA level) are not necessarily an indication to change antiretroviral therapy; such patients warrant close monitoring to determine whether maximal antiretroviral therapy benefit has been achieved.

OIs that occur in patients with virologic failure, defined as either the inability to suppress HIV RNA level after 12 weeks to 24 weeks of antiretroviral therapy or as a rebound of HIV RNA level after a period of suppression despite adequate adherence, indicate the need to reassess the antiretroviral

Table 3. Summary Recommendations On When to Initiate Antiretroviral Therapy in Antiretroviral Therapy–Naïve Patients With an Acute Opportunistic Infection (OI)

In the absence of compelling contraindications, early initiation of antiretroviral therapy near the time of initiating OI treatment should be considered for most patients with an acute OI, excluding tuberculosis (TB).

Other elements that should be considered when making this decision are degree of immunosuppression, availability of effective therapy for the OI, risk of drug interactions, overlapping drug toxicities, risk of developing immune reconstitution inflammatory syndrome (IRIS) and associated consequences, and willingness of the patient to adhere to the drug regimens.

In cases of cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy, Kaposi sarcoma, *Pneumocystis pneumonia*, and invasive bacterial infections, the early benefits of antiretroviral therapy outweigh the risk related to these other factors, and antiretroviral therapy should be started as soon as possible.

In the setting of TB disease, the following guidance for initiating antiretroviral therapy should be considered:

CD4+ count < 100 cells/μL	After 2 weeks (during intensive phase of therapy)
CD4+ count 100-200 cells/μL	After 2 months (at end of intensive phase of therapy)
CD4+ count sustained > 200 cells/μL	After 2 months (during maintenance phase of therapy)
CD4+ count sustained > 350 cells/μL	After completing TB therapy

Adapted from Kaplan et al, *Morb Mortal Wkly Rep*, 2009.

therapy. OIs occasionally occur in patients with robust CD4+ counts and suppressed HIV RNA levels; there is no evidence that changing or enhancing antiretroviral therapy in such cases is beneficial. Likewise, data are lacking with regard to the optimal management of patients who develop OIs in the context of discordant immunologic and virologic responses.

Opportunistic Infections During Pregnancy

There are few studies of the effects of interventions to prevent and treat OIs in HIV-infected pregnant women and their fetuses. The guidelines review available information about the physiologic changes pregnant women experience that might affect the efficacy or toxicity of drugs used to treat each OI. They also include information on the risks to the fetus of exposure to these agents and to radiation from diagnostic procedures. The guidelines emphasize the importance of focusing on the health of the mother as well as the child.

Prevention of Opportunistic Infections with Chemoprophylaxis

Chemoprophylaxis to prevent first episodes of OIs (primary prophylaxis) and to prevent OI recurrences and relapses (secondary prophylaxis, also called chronic maintenance therapy) remains essential for patients (1) who are not taking antiretroviral therapy or who have recently initiated antiretroviral therapy and still have a CD4+ count below the recommended thresholds for chemoprophylaxis, (2) who are unable to achieve a CD4+ count above these thresholds despite antiretroviral therapy, or (3) whose CD4+ count has fallen below these thresholds in association with virologic failure. For most pathogens, there have been no major changes in the drugs recommended for chemoprophylaxis or in the CD4+ count thresholds for initiating, discontinuing, or reinitiating chemoprophylaxis.

For patients resident in areas of the United States endemic for coccid-

iodomycosis, the guidelines now suggest that prophylaxis with fluconazole or itraconazole be considered for persons seropositive for anticoccidioidal IgG or IgM who have a CD4+ count below 250 cells/μL. Experts also suggest that annual serologic testing might be appropriate for patients previously seronegative for these immunoglobulins.

Prevention of Opportunistic Infections with Immunizations

As in previous guidelines, administration of 23-valent polysaccharide pneumococcal vaccine (PPV) is recommended to prevent pneumococcal disease in persons with a CD4+ count of 200 cells/μL or higher, unless the patient has received this vaccine within the prior 5 years. PPV should be offered to patients with a CD4+ count below 200 cells/μL as well. Because the vaccine's efficacy in this latter patient population is not well documented, revaccination after achieving a CD4+ count of at least 200 cells/μL can be considered. The duration of the protective effect of primary pneumococcal vaccination is unknown; the guidelines note that revaccination every 5 years may be considered, although definitive data on the clinical benefit of this intervention are lacking.

Annual administration of the inactivated influenza vaccine is also recommended to reduce the risk of influenza and of postinfluenza bacterial pneumonia. Administration of the live influenza vaccine is not recommended for HIV-infected patients. Given the prominence of influenza infections domestically and globally since the guidelines were formulated and data that suggest influenza illness might be more severe in HIV-infected patients than in HIV-uninfected patients,¹⁴⁻¹⁶ influenza vaccination with inactivated vaccine products as they become available seems especially relevant.

The guidelines suggest that administration of varicella vaccine be considered for those rare HIV-infected adults who are seronegative against varicella-zoster virus (VZV) and have a CD4+ count above 200 cells/μL. Routine serologic testing to determine the VZV

serostatus of HIV-infected adults is not recommended but might be indicated under certain circumstances (ie, HIV-infected contact of a person with active VZV infection). For patients who are VZV seronegative and have been exposed to VZV infection, especially chicken pox (which poses higher risk than localized herpes zoster), varicella-zoster immune globulin should be administered within 96 hours of exposure.

Despite substantial interest regarding the use of vaccines against herpes zoster and against human papillomavirus (HPV) in HIV-infected persons, data on the safety, immunogenicity, and efficacy of these vaccines are inadequate to support a recommendation for or against their use. Administration of HPV vaccine is considered optional for women aged 15 years to 26 years. The guidelines recommend that the herpes zoster vaccine not be administered to HIV-infected persons until additional data are available.

Hepatitis B Virus Infection

In this revision, guidance on the prevention and treatment of HBV coinfection in HIV-infected persons has been substantially expanded. The guidelines emphasize the importance of screening all patients for HBV infection. Up to 90% of certain HIV-infected populations (eg, intravenous drug users) can have at least 1 serum marker of previous exposure to HBV, and approximately 10% of HIV-infected patients have evidence of chronic HBV coinfection. HBV disease is accelerated in HIV-infected patients compared with HIV-uninfected patients, and HBV- and HIV-coinfected patients who start antiretroviral therapy without concurrent anti-HBV treatment, for instance if their HBV-infection is undetected, can experience substantial flares in hepatic transaminase levels and hepatic necrosis.

Clinicians should consider confirmatory HBV DNA screening for persons who test positive only for anti-HBV core antibody (anti-HBc) because false-positive anti-HBc test results appear to be more common in HIV-infected persons, especially those coinfecting with HCV. Administration of HBV vaccine is rec-

ommended for all HIV-infected persons who have no serologic evidence of HBV exposure (ie, negative for HBV surface antigen, anti-HBV surface antibody, and anti-HBc). Patients testing positive solely for anti-HBc can be given the complete primary vaccine series; however, some specialists would test for HBV DNA to rule out HBV infection. Patients without detectable HBV DNA should be vaccinated. Despite evidence that serologic responses to vaccination are improved at higher CD4+ counts, vaccination should not be deferred for susceptible persons while awaiting a rise in CD4+ count. Serologic responses should be checked 1 month after completing the vaccine series for all patients; if no response is observed, revaccination should be considered. Some experts recommend vaccinating patients, both for initial vaccination and for revaccination, with double doses of vaccine.

Guidance on the treatment of HBV infection in these guidelines has been harmonized with parallel guidance in the antiretroviral treatment guidelines disseminated by the US Department of Health and Human Services¹⁷ and by the International AIDS Society–USA panel.¹⁸ Dually infected patients who require anti-HBV therapy should be given highly active combination antiretroviral therapy for HIV infection regardless of their CD4+ count. The guidelines review in detail the available anti-HBV agents and stress the importance of using at least dual combination therapy against HBV as part of the HIV antiretroviral regimen. For HBV-infected patients who require anti-HBV therapy but who wish to defer therapy for HIV infection, drugs active solely against HBV should be selected to prevent emergence of antiretroviral drug resistance. The advantages and disadvantages of liver biopsy for patient management are discussed, and guidance is provided for individualizing the decision to perform liver biopsy.

Tuberculosis

Guidance on prevention and treatment of tuberculosis (TB) has been expanded substantially, in particular the recom-

mendations on the diagnosis of latent TB and issues related to coadministration of antiretroviral therapy and anti-TB therapy. The importance of testing all HIV-infected persons for latent TB disease is emphasized, even though TB remains an uncommon OI in the United States. This update provides new information comparing the traditional tuberculin skin test (TST) with recently available interferon gamma release assays (IGRA) for the diagnosis of TB. A detailed comparison of these tests is provided in Table 10 of the guidelines document. Evidence suggests that the IGRAs have more consistent and higher specificity than the TST, better correlation with surrogate measures of exposure to *Mycobacterium tuberculosis*, and less cross-reactivity because of BCG vaccination or other nontuberculous mycobacteria exposure. However, results from comparative studies of TST and IGRAs in HIV-infected patients indicate that concordance between the tests is not complete.

Discussions regarding the diagnosis of active TB with nucleic acid amplification testing of sputum smears have been updated and aligned with recent general TB management guidelines.¹⁹ The guidelines now recommend 9 months of isoniazid as preferred therapy for the treatment of latent TB and specifically note that the 2-month regimen of pyrazinamide plus rifabutin should no longer be offered.

Updated Information on Drug Interactions

The tabulated drug information in the guidelines has been extensively updated. Table 5 of the guidelines document summarizes toxicities of drugs used to treat and prevent OIs by drug class; Table 6 of the guidelines document summarizes the numerous known pharmacokinetic interactions between drugs used to treat and prevent OIs and antiretroviral drugs; and Table 7 of the document summarizes combinations of antiretroviral and other anti-infective drugs that should be avoided. Data in these tables on drug interactions affecting use of rifamycins for prevention and treatment of TB have been particularly improved.

Geographic Opportunistic Infections

Geographic OIs (ie, OIs that occur predominantly in regions outside the United States) deserve special attention. As life expectancy for HIV-infected patients receiving antiretroviral therapy increases, more Americans with HIV are travelling overseas. In addition, a substantial number of immigrants with HIV infection come to the United States from tropical countries and may present with OIs not typically seen here. Malaria, penicilliosis, leishmaniasis, trypanosomiasis, and isosporiasis are included. Clinicians in the United States need to be familiar with the diagnosis and management of these OIs in the presence of HIV infection.

Future Directions

Although clinical experience regarding the prevention and treatment of OIs has increased dramatically since the 1980s, important knowledge gaps remain. Effective programs must be identified and established to identify persons as early as possible after HIV infection has occurred and to link them to and retain them in care. Simpler, less invasive, and more rapid diagnostic methods are still needed for many OIs. Such diagnostics would have considerable value for resource-poor settings outside the United States, where our understanding of the spectrum of OIs and their empiric treatment remains limited. The safety and effectiveness of new vaccines, especially for infections such as HPV and herpes zoster that cause substantial morbidity among HIV-infected persons, remain largely unknown. Effective treatments for some OIs such as PML and cryptosporidiosis are still needed. Consideration is also being given to maintaining these guidelines in an online format with more frequent updates so that clinicians can have access to pivotal new information in the timeliest fashion possible.

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