

# HIV-Associated Opportunistic Infections—Going, Going, But Not Gone: The Continued Need for Prevention and Treatment Guidelines

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In the United States, the incidence of HIV-associated opportunistic infections (OIs) has decreased dramatically. The trend observed in the Centers for Disease Control and Prevention (CDC)-sponsored HIV Outpatient Study—a prospective, observational cohort study involving >8500 HIV-infected persons in 9 US cities who have received routine outpatient care (figure 1)—is typical of trends seen in many other clinical and research cohorts and medical practices. These reductions have resulted, in part, from improvements in and the diffusion of effective OI prophylaxis, but most importantly, they have resulted from the advent of combination antiretroviral therapy. It is not uncommon now for some medical residents and infectious diseases fellows to have never seen a case of cytomegalovirus retinitis or cryptosporidial diarrhea in an HIV-infected patient. As antiretroviral therapy becomes simpler, more potent, and less toxic, and

as our clinical concerns focus increasingly on the growing number of non-HIV-associated complications of HIV infection, we might be falsely reassured that OIs are soon to become a thing of the past.

OIs are here to stay, and they will continue to demand our attention for the foreseeable future. What has changed is the location in the health care system where clinicians now encounter them. Before effective combination antiretroviral therapy became available, OIs were common among HIV-infected persons receiving outpatient care. Today, the patients in the waiting rooms of many HIV clinics are often doing well with regard to the management of their infection. They experience conditions that are more typical of what would be encountered in a general internal medicine practice or that are related to chronic coinfections, such as hepatitis B and C virus coinfection. So where do OIs now occur in the United States? They occur among patients who are unaware that they have HIV infection who present for emergency or urgent care with an OI as the initial indicator of late-stage disease; among patients who, despite awareness of their HIV infection status, remain unlinked to care or, if receiving care, do not take or are unable to take antiretroviral therapy because of psychosocial or economic factors; and among patients who are receiving care and who, despite receiving antiretroviral therapy, do

not attain adequate virologic and immunologic response because of poor adherence to therapy, extensive antiretroviral resistance, or unexplained biological factors. Finally, they continue to occur among patients for whom we fail to initiate or reinstate prophylaxis when such is indicated by the patients' CD4 cell counts. Thus, although many reports have documented longer durations of survival and shifts in the burden of disease toward more-chronic, HIV-unrelated medical conditions, OIs remain a leading cause of hospitalization and death among HIV-infected persons [1–5].

Clinicians caring for HIV-infected patients must remain knowledgeable about optimal strategies for prevention and management of OIs to provide comprehensive, high-quality care. Later this year, the CDC's *Morbidity and Mortality Weekly Report* will publish the "Guidelines for Prevention and Treatment of Opportunistic Infections (OIs) Among HIV-Infected Adults and Adolescents." These guidelines were released online in draft form on 18 June 2008, and they both update and combine into one document the previously separate guidelines for prevention and for treatment of OIs published in 2002 and 2004 [6], respectively. The guidelines are jointly authored by the National Institutes of Health, the CDC, and the HIV Medical Association of the Infectious Diseases Society of America and

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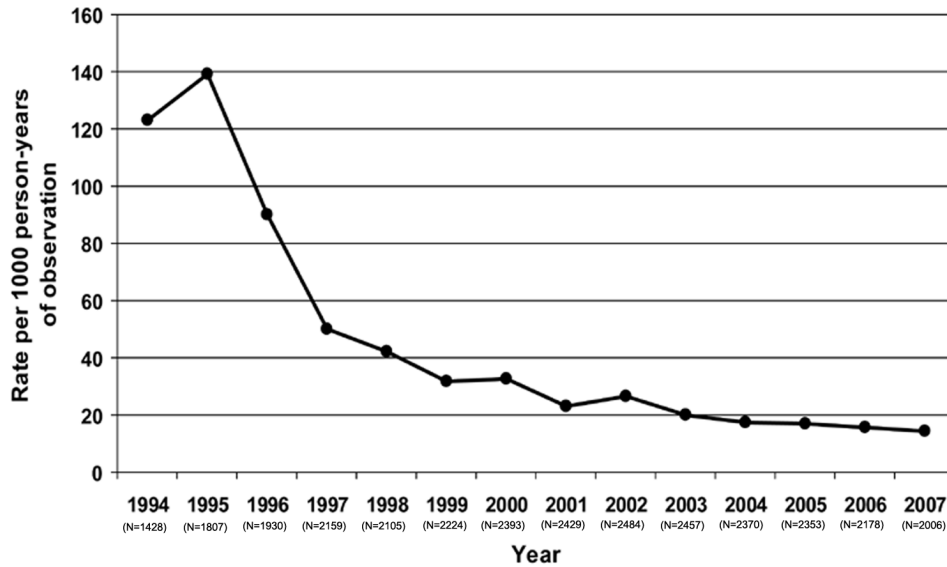
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**Figure 1.** Incidences of first AIDS-defining opportunistic infection, according to year, among all patients in care, HIV Outpatient Study, 1994–2007 (Centers for Disease Control and Prevention, unpublished data; courtesy of R. Baker and K. Buchacz).

include the voluntary contribution of >140 content-area experts. The genesis for these guidelines was the publication of 2 reports in *Morbidity and Mortality Weekly Report* in 1989 and 1993 that disseminated recommendations for prophylaxis against *Pneumocystis jirovecii* (formerly *carinii*) pneumonia [7] and *Mycobacterium avium* complex infection [8], respectively. In 1995, the first version of the present document that was expanded to encompass all HIV-related OIs was published in *Morbidity and Mortality Weekly Report* [9]. Revisions were published in 1997, 1999, and 2002 [10–12] and were reproduced, in whole or in part, in *Clinical Infectious Diseases*, *Annals of Internal Medicine*, and *American Family Physician*; accompanying editorials appeared in *JAMA*. These guidelines will remain an essential resource for HIV care providers in 2009. During the period from 18 June 2008 through 31 October 2008, they were downloaded >900,000 times (R. Heier, AIDSinfo; personal communication). When printed, these guidelines will be the largest document ever disseminated by *Morbidity and Mortality Weekly Report*.

The 2008 revision contains a number of notable changes and updates. There is

more emphasis placed on the importance of effective antiretroviral therapy for prevention and treatment of OIs, especially for OIs for which specific chemoprophylaxis and treatment do not exist. Each chapter is arranged according to a uniform order of subsections: “Epidemiology,” “Clinical Manifestations,” “Diagnosis,” “Preventing Exposure,” “Preventing Disease,” “Treatment of Disease,” “Monitoring and Adverse Events,” “Management of Treatment Failure,” “Preventing Recurrence,” “Discontinuing Secondary Prophylaxis,” and “Special Considerations During Pregnancy.” Of note, the subsection on monitoring and adverse events has been updated to contain additional material on the diagnosis and management of immune reconstitution inflammatory syndromes relevant to each OI. The chapter about tuberculosis now includes information on IFN- $\gamma$  release assays for the detection of latent *Mycobacterium tuberculosis* infection. The drug interaction tables have been updated to reflect the most recently available data, a new chapter has been added on hepatitis B virus infection, and malaria has been added to the chapter about OIs of geographic interest (i.e., OIs that may be acquired abroad and affect

persons receiving care in the United States).

The future of OI prevention and treatment will remain challenging. In the era of HAART, the proportion of persons with an AIDS-defining condition or a CD4 cell count <200 cells/mm<sup>3</sup> at the time at which HIV infection is diagnosed has been 25%–50% in selected rural and urban jurisdictions from which data have been reported [13–18]. For health care centers with available prospective data, the numbers do not appear to be improving, and a report from an inner-city, urban HIV-specialty clinic noted that the median CD4 cell count at presentation for care has been decreasing [19]. Although these data are consistent with the effects of delayed testing and entry to care, the possibility that these changes may also reflect increasing virulence among circulating strains of HIV as the epidemic matures cannot be ruled out [20, 21].

Whatever the underlying cause, reducing the number of late-stage diagnoses of HIV infection through earlier and more-widespread testing could substantially reduce the burden of OIs. However, during 2001–2006, the rates of HIV testing in the United States remained unacceptably low

and flat: ~40% of surveyed adults aged 18–64 years had ever been tested, and <25% of adults at risk of acquiring HIV infection had been tested in the preceding 12 months [22]. Since 2006, the CDC has endorsed efforts to rapidly increase the rate of HIV testing by streamlining the consent process, expanding opt-out testing to all health care settings, and screening persons at high risk of acquiring HIV infection annually [23]. Effective programs must be identified and established to link and retain persons in care as early as possible after infection has occurred. Improved diagnostic methods and treatments for OIs are still needed, and the efficacy of some existing vaccines (e.g., herpes zoster and human papillomavirus vaccines) in preventing OI remains unknown and deserves additional research. Because the number of persons living with HIV infection in the United States continues to increase, and as clinicians knowledgeable about the treatment of prevention of OIs age and retire, pressure mounts on our health care education and training programs to sustain an adequate number of health care providers who are competent in the management of HIV-associated OIs. The incidence of OI may be decreasing, but OIs are not gone, and the need for timely, evidence-based guidelines to maximize prevention strategies and to promptly recognize, accurately diagnose, and properly treat and manage OIs remains.

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## References

- Bonnet F, Lewden C, May T, et al. Opportunistic infections as causes of death in HIV-infected patients in the HAART era in France. *Scand J Infect Dis* 2005; 37:482–7.
- Gebo KA, Fleishman JA, Moore RD. Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states. *J Acquir Immune Defic Syndr* 2005; 40:609–16.
- Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006; 43:27–34.
- Smit C, Geskus R, Walker S, et al. Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion. *AIDS* 2006; 20:741–9.
- Buchacz K, Baker RK, Moorman AC, et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994–2005. *AIDS* 2008; 22:1345–54.
- Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. 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. Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr5315.pdf>. Accessed 13 January 2009.
- Centers for Disease Control and Prevention. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep* 1989; 38(Suppl 5):1–9.
- US Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium* Complex. Recommendations on prophylaxis and therapy for disseminated *Mycobacterium avium* complex for adults and adolescents infected with human immunodeficiency virus. *MMWR Recomm Rep* 1993; 42(RR-9):14–20. Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr4209.pdf>. Accessed 13 January 2009.
- US Public Health Service, Infectious Diseases Society of America. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. *MMWR Recomm Rep* 1995; 44(RR-8):1–34. Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr4408.pdf>. Accessed 13 January 2009.
- US Public Health Service/Infectious Diseases Society of America Prevention of Opportunistic Infections Working Group. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR Recomm Rep* 1997; 46(RR-12):1–46. Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr4612.pdf>. Accessed 13 January 2009.
- US Public Health Service, Infectious Diseases Society of America. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR Recomm Rep* 1999; 48(RR-10):1–59, 61–6. Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr4810.pdf>. Accessed 13 January 2009.
- Kaplan JE, Masur H, Holmes KK. 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 Recomm Rep* 2002; 51(RR-8):1–52. Available at: <http://www.cdc.gov/mmwr/PDF/rr/rr5108.pdf>. Accessed 13 January 2009.
- Sackoff JE, Shin SS. Trends in immunologic and clinical status of newly diagnosed HIV-positive patients initiating care in the HAART era. *J Acquir Immune Defic Syndr* 2001; 28:270–2.
- Centers for Disease Control and Prevention. Late versus early testing of HIV—16 sites, United States, 2000–2003. *MMWR Morb Mortal Wkly Rep* 2003; 52:581–6.
- Schwarcz S, Hsu L, Dilley JW, Loeb L, Nelson K, Boyd S. Late diagnosis of HIV infection—trends, prevalence, and characteristics of persons whose HIV diagnosis occurred within 12 months of developing AIDS. *J Acquir Immune Defic Syndr* 2006; 43:491–4.
- Mugavero MJ, Castellano C, Edelman D, Hicks C. Late diagnosis of HIV infection: the role of age and sex. *Am J Med* 2007; 120:370–3.
- Lyons MS, Lindsell CJ, Hawkins DA, Raab DL, Trott AT, Fichtenbaum CJ. Contributions to early HIV diagnosis among patients linked to care vary by test measure. *BMC Public Health* 2008; 8:220–30.
- Gandhi NR, Skanderson M, Gordon KS, Concato J, Justice AC. Delayed presentation for human immunodeficiency (HIV) care among veterans. *Med Care* 2007; 45:1105–9.
- Keruly JC, Moore RD. Immune status at presentation to care did not improve among antiretroviral-naïve persons from 1990 to 2006. *Clin Infect Dis* 2007; 45:1369–74.
- Dorrucchi M, Rezza G, Porter K, Phillips A; The Concerted Action on Seroconversion to AIDS and Death in Europe Collaboration. Temporal trends in postseroconversion CD4 cell count and HIV load: The Concerted Action on Seroconversion to AIDS and Death in Europe Collaboration, 1985–2002. *J Infect Dis* 2007; 195:525–34.
- Crum-Cianflone NE, Eberly L, Zhang Y, et al. Is HIV becoming more virulent? Initial CD4 cell counts among HIV seroconverters across the HIV epidemic: 1985–2007 [abstract H-4051]. In: Program and abstracts of the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy and the Infectious Diseases Society of America 46th Annual Meeting. (Washington, DC). Washington, DC: American Society for Microbiology; and Alexandria, VA: Infectious Diseases Society of America, 2008.
- Centers for Disease Control and Prevention. Persons tested for HIV—United States, 2006. *MMWR Morb Mortal Wkly Rep* 2008; 57:845–9.
- Branson BM, Hunter Handsfield H, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Morb Mortal Wkly Rep* 2006; 55(RR014):1–8, 9–16.