Introduction to the 1999 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus

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Opportunistic infections (OIs) are well recognized to produce substantial morbidity and mortality among patients with HIV infection. Since measures are available for reducing the incidence and the impact of these processes for patients, the United States Public Health Service and the Infectious Diseases Society of America, with endorsing professional societies, have developed guidelines for implementing a comprehensive strategy to prevent these OIs. These guidelines have been developed by a diverse working group of expert health care providers and patient representatives in order to synthesize available data and to provide practical advice for health care practitioners and patients.

Guidelines for the prevention of opportunistic infection (OI) in patients with HIV infection were first published in 1989, when it became apparent that clinicians and health care providers were not sufficiently familiar with the benefits of implementing chemoprophylaxis against Pneumocystis carinii pneumonia (PCP). Such prophylaxis could reduce morbidity and prolong survival, but it was evident that many practitioners were not introducing this prophylaxis into their standard strategies.

In 1989, several principles were established to guide the development of these guidelines, and they continue to be adhered to: (1) the guidelines should be developed by a diverse working group that includes well-informed health care professionals and patient representatives; (2) the guidelines should be based on available data that are sufficiently detailed to allow appropriate analysis; (3) guidelines should be written in a format that is focused and organized for practicing clinicians; (4) the strength of each recommendation should be clearly indicated by use of a defined rating system; (5) consensus should be sought from as many professional societies and governmental agencies as feasible, to help ensure that the guidelines are widely accepted; (6) the guidelines should be disseminated rapidly and widely; (7) guidelines should be revised as frequently as necessary to remain current.

In 1993, guidelines for preventing disseminated Mycobacterium avium complex were added to PCP guidelines. In 1995, when the Infectious Diseases Society joined the United States Public Health Service in sponsoring these guidelines, they were expanded to include all HIV-related OIs for which preventive methods were likely to be clinically beneficial. By 1997, knowledge about prevention had expanded rapidly, and the USPHS/IDSA Prevention of Opportunistic Infections Working Group again revised the guidelines. They have reached a wide audience, as assessed by the circulation of the journals where they were published, the number of reprint requests that were received, and surveys about health care provider awareness of the guidelines. Audits of patient records from clinics in a wide variety of settings also indicated that most recommendations rated A (“Should always be offered”) and I (“Evidence from at least 1 properly randomized controlled trial”) were offered to most patients.

In 1999, the influence of highly active antiretroviral therapy (HAART) on the incidence of OIs and the attributable decrease in morbidity and mortality have raised many issues about whether the guidelines should be modified. The most frequently asked questions concern whether there are sufficient data to warrant modifying the recommendations that primary and secondary prophylaxis, once instituted, should be maintained lifelong. Specifically, can primary or secondary prophylaxis be discontinued if patients respond to HAART with substantial increases in their CD4+ T lymphocyte counts? Questions also arose about the strength of evidence favoring implementation of newer “short course” regimens for prophylaxis of tuberculosis. Therefore, the Working Group was reconvened on 4–5 March 1999 to consider data collected since 1997, including information relevant to HAART and to other specific interventions, that might warrant changes in the guidelines.

The guidelines in this issue of Clinical Infectious Diseases [1] have already been posted on government web sites and printed in Morbidity and Mortality Weekly Report [2]. After the publication of past guidelines, some health care providers wanted more background information with which they could...
determine the relative importance of various interventions. This supplement in *Clinical Infectious Diseases* provides such background, much like similar supplements issued with the guidelines in 1995 and 1997. This preface summarizes the major changes in the guidelines, and following the guidelines are several articles that provide additional information about areas that have undergone the most change since 1997.

**The Effects of HAART**

The reduction in incidence of OIs among patients who have had a substantial immunologic response to HAART has persuaded some patients and some health care practitioners to advocate stopping primary or secondary prophylaxis in selected patients. Is this wise?

Since these guidelines are strongly data-driven, the Working Group assessed what studies were available to support the safety of stopping primary or secondary prophylaxis. Although considerable data will emerge in the next few years, the Working Group’s assessment was that, as of mid-1999, sufficient data to support stopping prophylaxis was only available for primary PCP and *Mycobacterium avium* complex (MAC) prophylaxis, and for secondary prophylaxis of cytomegalovirus (CMV) retinitis. Although stopping prophylaxis for other pathogens may be logical and reasonable, without data to support the safety of such a strategy, it was deemed imprudent to recommend stopping prophylaxis in those situations. Guidelines for stopping and restarting prophylaxis are summarized in table 14 in the USPHS/IDSA guidelines [1].

**PCP**

Primary prophylaxis continues to be indicated for all patients whose CD4+ T lymphocyte counts are <200/µL and for patients who have a history of oropharyngeal candidiasis. Specific indications for initiating prophylaxis are summarized for adults in table 3 (primary prophylaxis) and table 4 (secondary prophylaxis), and indications for children are summarized in table 12 (primary prophylaxis) and table 13 (secondary prophylaxis) in [1]. New recommendations suggest that there are additional criteria that should be considered for initiating primary prophylaxis. Recent data would suggest that patients who have a history of any AIDS defining illness and do not otherwise qualify for prophylaxis also warrant consideration, as do patients whose absolute CD4+ T lymphocyte count is >200/µL but whose CD4+ percentage is <14. If the CD4+ T lymphocyte count cannot be monitored every 3 months, initiation of prophylaxis at a CD4+ T lymphocyte count of <250/µL should be considered.

Secondary prophylaxis should still be offered to all patients who have had a previous episode of PCP. The preferred drug for primary or secondary prophylaxis continues to be trimethoprim-sulfamethoxazole (TMP-SMZ). The preferred dose is 1 double-strength tablet daily. For patients who have trouble tolerating TMP-SMZ, it may be helpful to reduce the dose to 1 single strength tablet daily, to use 1 double strength tablet 3 times weekly, or to use a gradual dose escalation regimen. Dapsone or dapsone-pyrimethamine are the first choice for alternative regimens. Atovaquone or aerosolized pentamidine can also be used.

Can primary or secondary PCP prophylaxis be stopped for patients who have responded to HAART by increasing their CD4+ T lymphocyte counts substantially? The Working Group assessed 4 studies of patients who initially met criteria for receiving primary PCP prophylaxis, but whose CD4+ T lymphocyte counts then responded to HAART by increasing to >200/µL. Data from these studies were deemed sufficient by the Working Group to merit a recommendation that clinicians can consider stopping primary PCP if the CD4+ T lymphocyte count of patients receiving HAART increased to >200/µL for at least 3–6 months. This recommendation is rated CII rather than A-level, because longer follow-up of these patients would be useful for assessing the degree of safety of this recommendation and because stopping TMP-SMZ will have only minimal impact on cost or pill burden.

Clinicians need to recognize that some patients who meet the criteria for stopping primary PCP prophylaxis could develop PCP, but the risk appears to be acceptably low. Primary prophylaxis should logically be restarted if the CD4+ T lymphocyte count again decreases to <200/µL.

The safety of stopping prophylaxis in HIV infected children has not been studied. Regarding secondary PCP prophylaxis, very few patients have been studied, so the safety of stopping secondary prophylaxis could not be adequately evaluated. Therefore, the Working Group elected to continue the recommendation that secondary PCP prophylaxis be maintained for life.

**Tuberculosis**

For patients with HIV infection who have a positive tuberculin skin test (TST; ≥5 mm of induration), there are new recommendations regarding the duration of therapy and the choice of agents. Nine months of isoniazid with pyridoxine is now considered to be acceptable, in contrast to the previous recommendation for 12 months of prophylaxis. Also, important new data suggest that an acceptable alternative is a 2-month regimen of rifamycin (either rifampin or rifabutin) plus pyrazinamide. However, drug interactions that involve the rifamycins are a particular concern, especially those that involve protease inhibitors, nonnucleoside reverse transcriptase inhibitors, sedatives, hypnotics, and cholesterol-lowering agents; these are detailed in tables 6 and 7 in [1].

Repeating the TST may be considered for patients whose
CD4+ T lymphocyte count is <200/µL when their TST is determined to be negative and whose CD4+ T lymphocyte counts increase to >200/µL. Anergy testing is not recommended to be performed routinely.

**MAC Infections**

Epidemiologic data indicate that the incidence of disseminated MAC disease has decreased markedly over the past 3 years. Based on this observation and 1 observational study, the Working Group deemed the data sufficient to recommend that primary prophylaxis for *M. avium intracellulare* be considered for discontinuation for patients whose CD4+ T lymphocyte counts increased to >100/µL for 3–6 months and who have sustained viral load suppression. Because this recommendation was based on the small amount of data available, it is rated CII.

Because of the paucity of data, the Working Group cannot at this time recommend that secondary prophylaxis (long-term maintenance therapy) be discontinued. The recommended regimen for secondary prophylaxis is a macrolide (either clarithromycin or azithromycin) plus ethambutol; rifabutin can be added as a third drug, although its contribution to efficacy is controversial.

**Bacterial Respiratory Infections**

As in previous guidelines, as soon as feasible after HIV infection is diagnosed, adults and adolescents who have CD4+ T lymphocyte counts ≥200/µL should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine, if they have not received this vaccine in the previous 5 years. Revaccination every 5 years may be considered. Revaccination should also be considered if the initial vaccination was administered when the patient’s CD4+ T lymphocyte count was <200/µL and if the count has since increased to >200/µL due to HAART.

TMP-SMZ and clarithromycin each provide antibacterial preventive activity, but neither should be prescribed specifically for that purpose except in unusual circumstances. For children with recurrent infections despite therapy with TMP-SMZ or clarithromycin, iv gamma globulin may be considered.

**Fungal Infections**

Routine primary prophylaxis for fungal infections is still not recommended. If recurrences of mucosal candidiasis are frequent, a variety of azole regimens are recommended. However, this might be problematic for pregnant women; the guidelines draw attention to reports that all systemic azoles may be embryotoxic.

For cryptococcal disease, secondary prophylaxis (maintenance therapy) is still recommended to be maintained lifelong, even for patients who have had excellent responses to HAART. This recommendation reflects the paucity of data about the safety of discontinuing secondary prophylaxis, rather than the knowledge that such an approach is unsafe.

For histoplasmosis, primary prophylaxis is still not recommended, despite the efficacy of itraconazole as a prophylactic agent against this pathogen. Secondary prophylaxis for histoplasmosis or coccidiomycosis should continue to be maintained lifelong for the same reasons that cryptococcal secondary prophylaxis should be continued.

**CMV, Herpes Simplex Virus (HSV), and Varicella Zoster Virus (VZV) Infections**

Primary prophylaxis for CMV, HSV, or VZV is still not recommended. For secondary prophylaxis of CMV retinitis, the new guidelines recommend that chemotherapy may be stopped if patients have CD4+ T lymphocyte counts >100–150/µL for 3–6 months, if they can be followed regularly by an ophthalmologist, if their lesions were not sight-threatening, and if vision in the other eye is adequate. This recommendation is rated CII because the studies reviewed are not large and many use historical controls. There are not enough data to venture an opinion about the safety of stopping secondary prophylaxis for patients with CMV disease other than retinitis.

Since 1997, additional information about famcyclovir and valacyclovir indicates that these agents can be alternatives to acyclovir for safe and effective long-term suppression of HSV in patients with frequent or severe recurrences.

**Human Herpesvirus 8 (HHV-8) and Hepatitis C (HCV) Infections**

These 2 pathogens are discussed for the first time in the 1999 guidelines. HHV-8 is included because this pathogen may be sexually transmitted and because some interventions may reduce the likelihood of transmission of this agent or the likelihood of development of Kaposi’s sarcoma. HHV-8 is associated with the development of Kaposi’s sarcoma. Epidemiologic data suggest that sexual transmission occurs among men who have sex with men. Latex condoms used during each act of sexual intercourse may prevent exposure to this pathogen. Therapy with ganciclovir or foscarnet is associated with lower rates of Kaposi’s sarcoma than is therapy without a systemic anti-CMV agent; however, until more information is available, no recommendation can be made concerning the use of these drugs for preventing Kaposi’s sarcoma.

Hepatitis C is a major cause of morbidity and mortality for some HIV infected patient populations. Specific steps can be taken to reduce transmission of HCV and the severity of HCV-induced liver disease.

The chief route of transmission of hepatitis C is injection
drug use. Therefore, cessation of illegal drug use or the use of clean paraphernalia when injecting or snorting illegal drugs probably will reduce the likelihood of transmission. Safe-sex practices may also decrease the risk of exposure.

All patients infected with HIV should be screened for HCV by use of a licensed immunoassay. If patients have undetectable antibody but have other evidence of chronic liver disease, they can be tested for the presence of HCV RNA in their blood.

Patients coinfected with HIV and HCV should reduce the risk of additional insults to their livers by receiving hepatitis A vaccine (if they have no history of hepatitis A and are seronegative for antibody to hepatitis A) and by avoiding excessive consumption of alcohol.

Patients coinfected with HIV and HCV should be considered for therapy, even though the long-term benefit of therapy has not yet been established.

References
