

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor***PROPHYLAXIS AGAINST
OPPORTUNISTIC INFECTIONS
IN PATIENTS WITH HUMAN
IMMUNODEFICIENCY VIRUS
INFECTION**

JOSEPH A. KOVACS, M.D., AND HENRY MASUR, M.D.

SOON after the acquired immunodeficiency syndrome (AIDS) was first described in 1981,¹⁻⁴ it became clear that opportunistic infections occurred with remarkable frequency and caused substantial morbidity and mortality among patients with AIDS. On the basis of a series of clinical trials, chemoprophylaxis to prevent initial episodes of certain opportunistic infections (primary prophylaxis) and subsequent episodes (secondary prophylaxis) became the standard of care. The success of highly active antiretroviral therapy (defined as combination antiretroviral regimens that include either a potent viral-protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor) in reducing the incidence of AIDS-related opportunistic infections and consequent morbidity and mortality has led to a reassessment of the role of prophylaxis against these infections in patients with human immunodeficiency virus (HIV) infection who have durable antiviral responses.⁵⁻⁸ The Public Health Service and the Infectious Diseases Society of America have recently published revised guidelines for the prevention of opportunistic infections in patients with HIV infection.⁹ In this review we provide a perspective on these guidelines and on the principles and recent developments that we think should form the basis for modifications in the approach to the prevention of both initial episodes and recurrences or relapses of these infections.

**CURRENT EPIDEMIOLOGY OF
OPPORTUNISTIC INFECTIONS**

Reports from individual institutions as well as large, multicenter studies have documented dramatic de-

creases in the occurrence of opportunistic infections since the introduction of combination antiretroviral regimens, especially regimens that include HIV-protease inhibitors.⁵⁻⁸ The declining incidence of virtually all opportunistic infections is highlighted by a recent report from the prospective observational Adult/Adolescent Spectrum of HIV Disease cohort study, which described the incidence of opportunistic infections from 1992 to 1997 in more than 22,000 patients, with nearly 36,000 person-years of follow-up.⁶ The incidence of all opportunistic infections decreased by 55 percent from 1992 to 1997 (highly active antiretroviral therapy first became commercially available in 1995). The percentage decline was steeper for some opportunistic infections, such as *Mycobacterium avium* complex and cytomegalovirus infections, than for others, such as *Pneumocystis carinii* infection (Fig. 1). Cytomegalovirus retinitis had the greatest rate of decline, and non-Hodgkin's lymphoma had the least among those reported elsewhere.¹¹⁻¹⁴ The variation among rates of decline in the incidence of specific opportunistic infections in patients receiving highly active antiretroviral therapy suggests that the immune reconstitution induced by this therapy does not protect equally against all opportunistic complications. However, other factors, such as greater use of antimicrobial prophylaxis or changes in diagnostic and therapeutic approaches, may also have a role in this variation.

In 1997, despite the reductions in the incidence of opportunistic infections attributed to highly active antiretroviral therapy, the absolute rates of these infections were still high. *P. carinii* pneumonia, for example, occurred at a rate of 46 cases per 1000 patient-years.⁶ In 1997 the lack of adherence to guidelines for the prevention of opportunistic infections,¹⁵ which have been published since 1989 for *P. carinii* pneumonia¹⁶ and since 1993 for *M. avium* complex infection,¹⁷ was substantial; among patients who met the criteria in the guidelines, 20 percent were not receiving prophylaxis against *P. carinii* pneumonia and more than 50 percent were not receiving prophylaxis against *M. avium* complex. These results suggest that a more vigorous focus on implementing strategies for the prevention of opportunistic infections could provide further clinical benefit.

Emphasis on specific measures to prevent opportunistic infections is important because of the limitations of highly active antiretroviral therapy. Although many patients benefit from antiretroviral therapy, not all patients are willing to take it, many patients cannot tolerate or adhere to the complex drug regimens that constitute this therapy, and immunity may not be restored to a level that substantially reduces the

From the Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Md. Address reprint requests to Dr. Masur at the National Institutes of Health, Clinical Center, Critical Care Medicine Department, 10 Center Dr., Bethesda, MD 20892-1662, or at hmasur@nih.gov.

©2000, Massachusetts Medical Society.

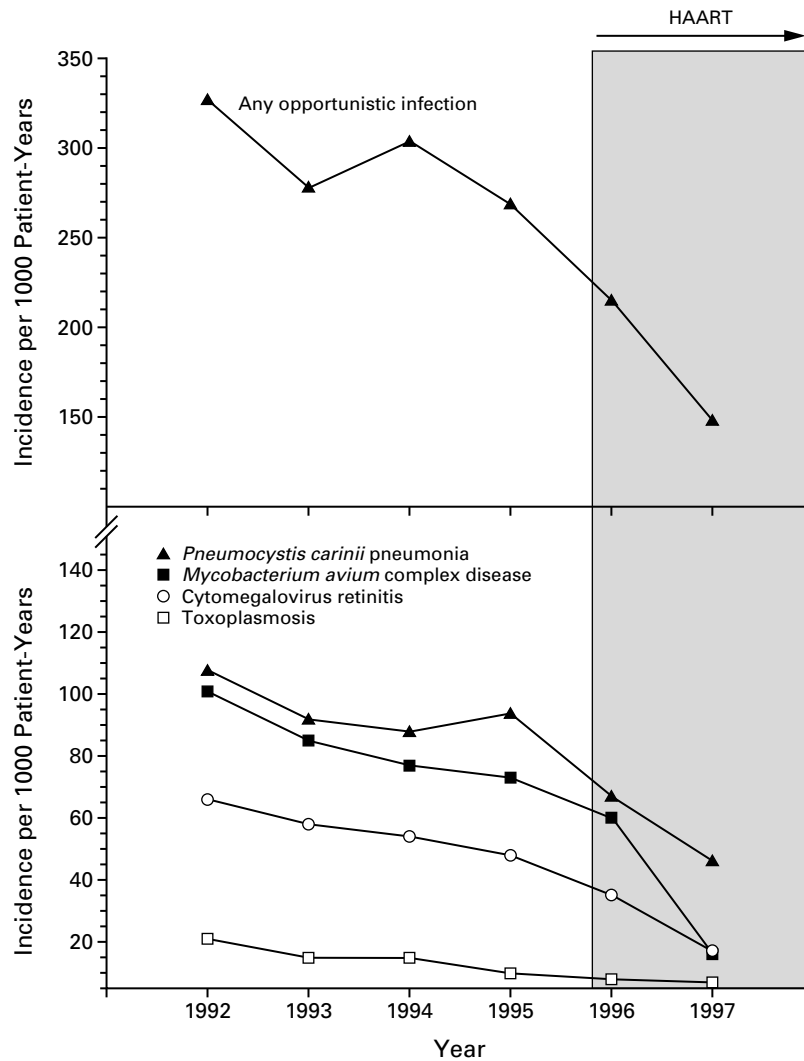


Figure 1. Incidence of Selected Opportunistic Infections in Patients with HIV Infection, 1992 through 1997, Based on Data from the Adult/Adolescent Spectrum of HIV Disease Cohort Study.⁶ The incidence of all opportunistic infections meeting the CDC criteria¹⁰ is shown in the upper panel, and the incidence of individual infections in the lower panel. The shaded areas indicate the period of wide availability of highly active antiretroviral therapy (HAART). The decline after 1995 reflects in large part the effect of highly active antiretroviral therapy.

risk of opportunistic infection. Furthermore, HIV is expected to develop resistance to current therapies in many patients (probably more than 50 percent) in whom highly active antiretroviral therapy is initially successful, with a subsequent decline in immunologic function and an increase in susceptibility to infection.⁸

IMMUNOLOGIC SUSCEPTIBILITY TO INFECTION

Susceptibility to opportunistic infections increases as HIV-induced immunodeficiency becomes more severe. Among patients with HIV infection, CD4 T-lymphocyte counts continue to be the best-vali-

dated predictors of the likelihood of an opportunistic infection. Although plasma viral levels independently provide important prognostic information with regard to the risk of AIDS,¹⁸⁻²⁰ the risk of specific opportunistic infections has not yet been adequately related to plasma viral levels. Thus, current guidelines⁹ for initiating prophylaxis do not include criteria based on plasma viral load.

To predict the likelihood of opportunistic infection and to initiate prophylaxis, most clinicians use the absolute CD4 cell count rather than the percentage of total lymphocytes that are CD4 cells. The percentage is directly measured and appears to be more re-

producibile; the absolute number is calculated from the percentage. However, almost all the clinical literature has focused on absolute CD4 cell counts, and therefore clinicians continue to use these counts. In some patients, the percentage of CD4 cells correlates better with susceptibility to infection than does the absolute CD4 cell count; these patients include pregnant women, young children, and patients who have undergone splenectomy.²¹⁻²³

In studies conducted before highly active antiretroviral therapy became available, patients with CD4 cell counts above 200 per cubic millimeter were found to be at low risk for the majority of AIDS-defining opportunistic infections.²⁴ In these studies, the risk of individual opportunistic infections increased in a hierarchical fashion relative to decreases in the CD4 cell count. Prospective and retrospective studies identified 200 CD4 cells per cubic millimeter as the level at which the incidence of *P. carinii* pneumonia became high enough that prophylaxis was warranted.^{16,24} Similar studies identified thresholds at which other opportunistic infections could be expected to occur with considerable frequency. For disease due to cytomegalovirus, *M. avium* complex, cryptosporidium, and toxoplasma, for example, this threshold was approximately 50 to 100 cells per cubic millimeter, considerably lower than the threshold for *P. carinii* pneumonia. For other opportunistic pathogens, such as *M. tuberculosis* and candida species, the threshold was considerably higher than for *P. carinii* pneumonia, and some candidal and tuberculosis disease occurred even in patients with high CD4 cell counts.

The profound immune reconstitution that occurs in patients treated with highly active antiretroviral therapy raises an important question: Has the relation between the CD4 cell count and the occurrence of opportunistic infections been altered by this treatment? Data from a variety of sources suggest that this relation has not changed in any obvious or substantial manner.

The EuroSIDA study (a prospective observational study involving approximately 7300 patients) examined the risk of AIDS-defining opportunistic infections or death in patients with CD4 cell counts above 200 per cubic millimeter as a function of the nadir CD4 cell counts (Fig. 2).²⁵ The incidence of infection in a multivariate analysis was about three times as high among patients with a nadir CD4 cell count of less than 150 per cubic millimeter as among patients with nadir CD4 cell counts above 150 per cubic millimeter. However, the incidence rates were much lower, regardless of the nadir value, among patients whose CD4 cell counts rose above 200 per cubic millimeter than among patients whose CD4 cell counts remained below 50 per cubic millimeter (3.7 to 8.1 vs. 72.9 episodes per patient-year). Thus, patients whose CD4 cell counts rise from below 200 per cubic millimeter to above 200 per cubic millimeter are sub-

stantially protected against opportunistic infections, regardless of how low the nadir CD4 cell count was.

If patients with CD4 cell counts above 200 cells per cubic millimeter are substantially protected from opportunistic infection, despite their previous nadir count, can those taking prophylactic regimens safely discontinue such therapy? Several prospective observational or controlled studies (summarized below) have demonstrated that specific prophylactic regimens can be safely discontinued in patients in whom CD4 cell counts have increased above the thresholds for initiating prophylaxis. Thus, even in patients with a substantially lower prior CD4 cell count, the most recent confirmed CD4 cell count continues to be the best predictor of the risk of opportunistic infections and should be used in making decisions about initiating or maintaining prophylactic regimens to prevent opportunistic infections.

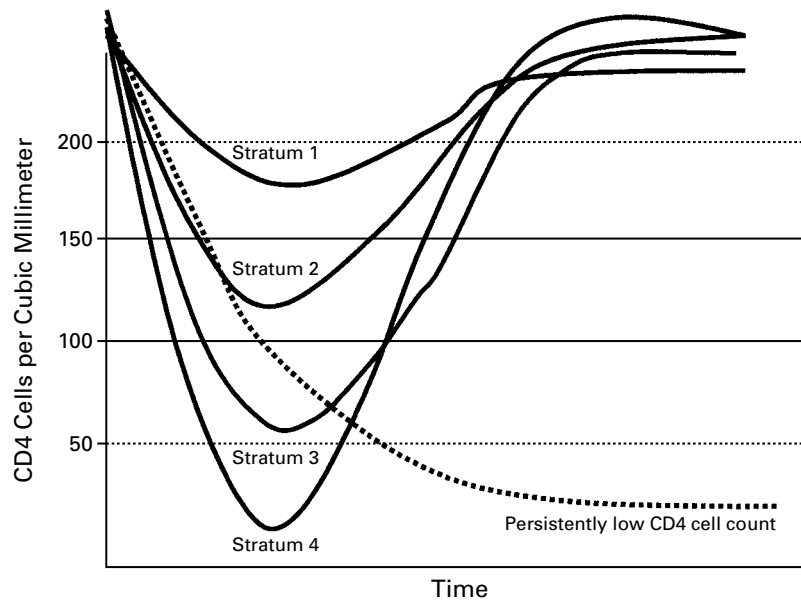
PREVENTION OF OPPORTUNISTIC INFECTIONS

Several principles can help guide the development of a clinical approach to preventing opportunistic infections. First, the incidence of opportunistic infections caused by certain nonubiquitous pathogens, which are acquired after HIV infection is recognized, can probably be reduced by avoiding exposure to the pathogen.

Second, as noted above, a recent CD4 cell count is the best predictor of immunologic susceptibility to opportunistic infection. However, the risk of opportunistic infection in relation to CD4 cell count varies continuously over the spectrum of CD4 cell counts rather than changing in an all-or-none manner. Figure 3 shows the CD4 cell counts within six months before an episode of *P. carinii* pneumonia in patients in the Multicenter AIDS Cohort Study during the era before antiretroviral therapy was available. Twenty-three percent of these cases of *P. carinii* pneumonia occurred in patients who did not meet the current CD4 cell criteria for initiating prophylaxis.

Third, no prophylactic intervention is 100 percent effective, and each intervention, whether it involves behavioral modifications, immunization, or chemoprophylaxis, has potential inconvenience, toxicity, environmental effect, or financial cost that must be weighed in considering whether the intervention is appropriate for an individual patient.

When a patient is first evaluated for HIV infection, screening is useful for determining prior exposure to certain pathogens. A tuberculin skin test should be performed in every patient with newly diagnosed HIV infection, except for those who already have had a positive test result. Testing should be repeated annually.²⁶ It is also useful to obtain an antitoxoplasma antibody test, an anticytomegalovirus antibody test,^{27,28} and serologic tests for hepatitis A, B, and C. In addition, a history of likely exposures, such as potential



GROUP	INCIDENCE RATE/100 PATIENT-YR
Response	
Stratum 1	3.7 (3.3–4.1)
Stratum 2	6.0 (3.4–10.0)
Stratum 3	8.1 (4.5–13.4)
Stratum 4	5.9 (3.0–10.2)
Persistently low CD4 cell count	72.9 (69.0–76.8)

Figure 2. Nadir CD4 Cell Counts and Incidence Rates of Opportunistic Infections in Patients with HIV Infection.

The data are from the EuroSIDA study.²⁵ Patients who had increases in CD4 cell counts to more than 200 per cubic millimeter in response to highly active antiretroviral therapy are grouped according to the lowest measured CD4 cell count. The values below the graph are the incidence rates for all opportunistic infections for the individual groups and, in parentheses, the 95 percent confidence intervals.

occupational exposure to tuberculosis or residence in or travel to areas where infection with histoplasma, coccidioides, various enteric pathogens, or vector-borne protozoa (e.g., leishmania or trypanosome species) is endemic, can help guide counseling.

Reduction of Exposure to Pathogens

Many AIDS-related opportunistic infections are caused by pathogens that are ubiquitous in the environment, and disease may occur because of continuous exposure (Table 1). Alternatively, pathogens that are either common or uncommon in the environment may cause disease by reactivation of a latent infection acquired in the past. For pathogens that are ubiquitous (e.g., *P. carinii* and *M. avium* complex), it is impractical to reduce exposure substantially. However, it is logical to avoid high-intensity exposure, such as sharing a room with a patient with active *P. carinii* pneumonia, in order to reduce the potential for reinfection with a new strain of *P. carinii*, since reinfection has been implicated in some cases.^{29,30}

Avoidance of exposure is feasible for some pathogens.³¹ Patients may benefit from counseling about the potential of acquiring tuberculosis in certain high-risk occupational settings, such as correctional facilities or health care facilities, and about avoiding exposure to certain enteric organisms from contact with young animals or consumption of unprocessed surface water (Table 1).

Immunization

Because of the frequency of pneumococcal respiratory infections, all patients with HIV infection should receive pneumococcal vaccine. The vaccine is inexpensive, easy to administer, and safe.^{32,33} Repeated immunization at least every three to five years may be beneficial, because antibody titers wane rapidly in patients with HIV infection.³⁴ Patients who were first immunized when their CD4 cell counts were below 200 per cubic millimeter should probably be reimmunized if the count increases above that value, although the increase in serum titers of

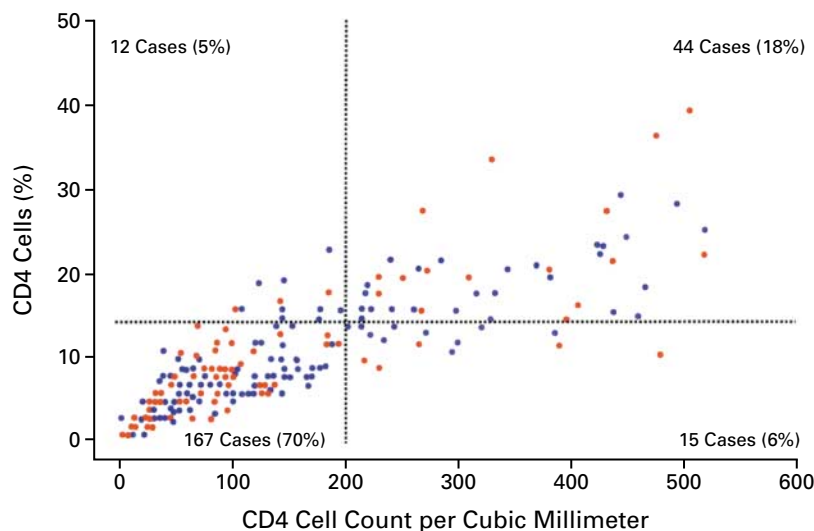


Figure 3. Cases of *Pneumocystis carinii* Pneumonia in Relation to Recent CD4 Cell Count. Each dot represents one of the 238 cases of *P. carinii* pneumonia in the Multicenter AIDS Cohort Study through July 1988, before the availability of antiretroviral drugs. The axes show the most recent CD4 cell counts (all within six months before the episode of *P. carinii* pneumonia). The number and percentage in each quadrant show the fraction of the 238 cases that fell within that quadrant of the graph. Cases indicated by a red dot represent patients who had either oral candidiasis or prolonged fever before having *P. carinii* pneumonia, and who therefore would have been identified as candidates for prophylaxis against *P. carinii* pneumonia independently of their CD4 cell counts. The dotted lines indicate the thresholds for initiating prophylaxis. Data courtesy of John Phair, M.D., and Alvaro Munoz, Ph.D., Multicenter AIDS Cohort Study.

TABLE 1. RECOMMENDATIONS FOR MINIMIZING EXPOSURE TO SELECTED PATHOGENS AMONG PATIENTS WITH HIV INFECTION.

PATHOGEN	POTENTIALLY EFFECTIVE INTERVENTION
<i>Pneumocystis carinii</i>	Avoid close contact with patients who have active <i>P. carinii</i> pneumonia (e.g., avoid sharing hospital room).
<i>Toxoplasma gondii</i>	Avoid eating undercooked red meat and exposure to cats that scavenge for food outdoors.
Cryptosporidium	Avoid drinking unprocessed ground water (e.g., from lakes or streams); use properly boiled, bottled, or filtered water; avoid household pets less than 6 months of age, especially those that were obtained from commercial breeders or pet shelters, that were previously strays, or that have diarrhea; emphasize good hygiene in child care.
<i>Mycobacterium tuberculosis</i>	Avoid high-risk occupational settings, such as correctional facilities, homeless shelters, and certain health care situations.
Cytomegalovirus	If patient is seronegative for cytomegalovirus, avoid transfusion with cytomegalovirus-seropositive or unfiltered blood products; avoid unprotected sexual exposure. Emphasize good hygiene in child care.
Human papillomavirus, herpes simplex virus, and hepatitis B	Avoid unprotected sexual exposure.
<i>Histoplasma capsulatum</i>	In areas of endemic disease, avoid high-risk activities such as exploring caves or cleaning chicken coops; avoid exposure to feces of wild birds.

IgG against specific pneumococcal strains may be marginal.³⁵

Patients who have no evidence of prior infection with hepatitis B and who are at risk for acquiring it should receive hepatitis B vaccine, especially if they are infected with hepatitis C. Because patients infected with hepatitis B or hepatitis C may be at increased risk for severe liver damage if they acquire hepatitis A,³⁶ they should receive hepatitis A vaccine if they are seronegative for hepatitis A. Although there is no evidence that influenza is more severe or more frequent in HIV-infected patients than in others, it is reasonable to recommend influenza vaccine annually.³⁷

There has been considerable discussion about the possibility that immunization could cause an increase in plasma HIV viral load by activating CD4 cells, which may increase the susceptibility of these cells to infection by HIV. However, there are no convincing data that immunization causes sustained or clinically important increases in plasma levels of HIV RNA.³⁷ Thus, immunization with killed microbial products or recombinant products is considered safe. Live-virus vaccines (e.g., oral poliovirus, measles, varicella, mumps, and yellow fever vaccines) should probably not be given to adults with HIV.

Susceptible patients (those who are seronegative for varicella-zoster or have no history of chickenpox

or shingles) who have been exposed to chickenpox or shingles should receive varicella–zoster immune globulin as soon as possible (but definitely within 96 hours) after exposure. The efficacy of preemptive therapy with acyclovir, famciclovir, or valacyclovir after exposure in these patients is unknown.

Primary Chemoprophylaxis

P. carinii

Primary prophylaxis against *P. carinii* pneumonia is indicated for patients with CD4 cell counts below 200 per cubic millimeter and for patients with a history of oropharyngeal candidiasis (Table 2).^{9,16,24} In patients with a history of substantial unexplained weight loss,³⁸ a prior AIDS-defining event,³⁹ unexplained fever for more than two weeks,²⁴ or a prior episode of any type of pneumonia,³⁹ prophylaxis should also be strongly considered. Initiating prophylaxis at CD4 cell counts below 250 per cubic millimeter may be more efficient in including patients at highest risk,³⁹ especially for patients with infrequent laboratory monitoring, a high plasma viral load (more than 10,000 to 20,000 copies per milliliter), or a recent steep decline in the CD4 cell count.

The regimen of choice for primary prophylaxis against *P. carinii* pneumonia is trimethoprim–sulfa-

methoxazole, either one double-strength tablet (80 mg of trimethoprim plus 400 mg of sulfamethoxazole) or one single-strength tablet (40 mg of trimethoprim plus 200 mg of sulfamethoxazole) daily.^{9,16,40-43} A trimethoprim–sulfamethoxazole regimen of one double-strength tablet three times weekly is not as effective as a daily regimen, although it is better tolerated.⁴⁴ Adverse reactions are common, but every effort should be made to continue prophylaxis because trimethoprim–sulfamethoxazole is more active against *P. carinii* pneumonia than alternative regimens, and it also provides protection against toxoplasmosis,⁴⁵ bacterial respiratory infections,⁴³ and possibly some enteric pathogens. If trimethoprim–sulfamethoxazole is discontinued because of a non–life-threatening adverse reaction, patients should be rechallenged with a regimen of gradual dose escalation.^{43,46,47}

Alternative antipneumocystis regimens with documented efficacy are summarized in Table 2.^{40-44,48-52} Concern about the development of resistance has arisen from reports of an increase in the frequency of mutations in the gene encoding *P. carinii* dihydropteroate synthase, the enzyme targeted by the sulfonamides. However, there is no clinical evidence that trimethoprim–sulfamethoxazole prophylaxis is becoming less effective.⁵³⁻⁵⁵

TABLE 2. DRUG REGIMENS FOR PRIMARY PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS IN PATIENTS WITH HIV INFECTION.

PATHOGEN	FIRST CHOICE	ALTERNATIVES
<i>Pneumocystis carinii</i>	Trimethoprim–sulfamethoxazole, 1 double-strength tablet orally per day or 1 single-strength tablet orally per day	Trimethoprim–sulfamethoxazole, 1 double-strength tablet orally 3 times a week; dapsone, 50 mg orally twice a day or 100 mg orally per day; dapsone, 50 mg orally per day, plus pyrimethamine, 50 mg orally once a week, plus leucovorin, 25 mg orally once a week; dapsone, 200 mg orally once a week, plus pyrimethamine, 75 mg orally once a week, plus leucovorin, 25 mg orally once a week; atovaquone, 1500 mg orally per day; aerosolized pentamidine, 300 mg monthly by Respigard II nebulizer
<i>Toxoplasma gondii</i>	Trimethoprim–sulfamethoxazole, 1 double-strength tablet orally per day	Trimethoprim–sulfamethoxazole, 1 single-strength tablet orally per day; dapsone, 50 mg orally per day, plus pyrimethamine, 50 mg orally once a week, plus leucovorin, 25 mg orally once a week; atovaquone, 1500 mg orally per day
<i>Mycobacterium tuberculosis</i>		
Isoniazid-sensitive source case (if known)	Isoniazid, 300 mg orally per day, plus pyridoxine, 50 mg orally per day, for 9 mo; isoniazid, 900 mg orally twice a week, plus pyridoxine, 100 mg orally twice a week, for 9 mo; rifampin, 600 mg orally per day, plus pyrazinamide, 20 mg/kg of body weight orally per day, for 2 mo	Rifabutin, 300 mg orally per day, plus pyrazinamide, 20 mg/kg orally per day, for 2 mo; rifampin, 600 mg orally per day for 4 mo
Isoniazid-resistant source case (if known)	Rifampin, 600 mg orally per day, plus pyrazinamide, 200 mg/kg orally per day, for 2 mo	Rifabutin, 300 mg orally per day, plus pyrazinamide, 20 mg/kg orally per day, for 2 mo; rifampin, 600 mg orally per day for 4–6 mo; rifabutin, 300 mg orally per day for 4–6 mo
Multidrug-resistant (isoniazid and rifampin)	Choice of drugs requires consultation with experts	None
<i>M. avium</i> complex	Azithromycin, 1200 mg orally once a week; or clarithromycin, 500 mg orally twice a day	Rifabutin, 300 mg orally per day; azithromycin, 1200 mg orally once a week, plus rifabutin, 300 mg orally per day

Toxoplasma gondii

Patients with serum antitoxoplasma antibodies are at risk for reactivated toxoplasmosis and should receive prophylaxis when their CD4 cell counts are less than 100 per cubic millimeter.⁹ The regimen of choice for primary prophylaxis against toxoplasmosis is trimethoprim–sulfamethoxazole (Table 2).^{27,45} The other antipneumocystis regimens listed in Table 2, except aerosolized pentamidine, are probably also effective against toxoplasma.^{27,49,50}

M. tuberculosis

Primary prophylaxis is indicated for patients with a positive tuberculin skin test (induration of more than 5 mm) who have never been treated for tuberculosis, and for patients with recent exposure to someone with active tuberculosis.²⁶ Unless the strain causing the index case is known to be drug-resistant, any of the regimens listed in Table 2 can be used.^{26,56–62} There has been considerable debate about the optimal duration of prophylaxis^{56–60}: a 9-month regimen was a consensus recommendation, because a 6-month regimen was less effective than longer regimens and regimens lasting more than 12 months did not appear to provide additional benefit.²⁶

Among HIV-related opportunistic infections, tuberculosis is unusual in that maintenance therapy (secondary prophylaxis) is not necessary after an adequate course of chemotherapy for active tuberculosis. Relapse is rare among patients with drug-sensitive *M. tuberculosis* infection; when subsequent episodes occur, some are clearly from reinfection rather than relapse.^{26,63}

Antituberculous treatment requires monitoring for drug interactions and toxicity. Isoniazid is hepatotoxic and should be used cautiously in patients with hepatitis B or hepatitis C and in patients receiving other potentially hepatotoxic drugs, such as HIV-protease inhibitors (especially ritonavir). In addition, interactions between rifamycins (rifampin, rifabutin, and rifapentine) and protease inhibitors or nonnucleoside reverse-transcriptase inhibitors can lead to reduced efficacy or increased toxicity of the antiretroviral regimen; rifampin should almost never be administered concurrently with these types of drugs, and rifabutin should be used cautiously.^{26,64}

***M. avium* Complex**

Primary prophylaxis against *M. avium* complex is indicated in patients with CD4 cell counts under 50 per cubic millimeter. Either azithromycin or clarithromycin is preferred over rifabutin because of their better efficacy and fewer drug interactions.^{9,65–67} Azithromycin can have adverse gastrointestinal effects, but the once-a-week regimen (1200 mg) is convenient, and this drug is associated with fewer drug interactions than clarithromycin, which must be taken twice daily. The combination of azithromycin plus

rifabutin is more effective than azithromycin alone, but the increase in efficacy is counterbalanced by the greater toxicity and drug interactions associated with rifabutin.⁶⁷ Like trimethoprim–sulfamethoxazole, clarithromycin and azithromycin appear to reduce the frequency of bacterial respiratory tract infections,^{65,67} and azithromycin may have antipneumocystis activity as well.⁶⁸

Other Infections

Primary prophylaxis is not routinely recommended against herpesviruses (cytomegalovirus, herpes simplex virus, and varicella–zoster virus) or fungi (candida species, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Coccidioides immitis*). Ganciclovir is probably effective for preventing cytomegalovirus disease,^{69,70} but oral ganciclovir is expensive, at least 12 large capsules must be taken per day, survival is not improved, and the development of ganciclovir-resistant herpesviruses is a concern. Fluconazole is effective for preventing both mucosal candidiasis and cryptococcosis,^{71–73} and itraconazole capsules are effective for preventing histoplasmosis and cryptococcosis, but not candidiasis.⁷⁴ However, the expense, inconvenience, and drug interactions associated with long-term azole therapy, as well as the potential promotion of azole-resistant candida species, make most clinicians reluctant to use azoles for primary prophylaxis. When candidal disease occurs, short-term therapy can be instituted with a high rate of success.

Secondary Prophylaxis

Lifelong secondary prophylaxis for severe or life-threatening opportunistic infections has generally been advocated because of their high recurrence rates (Table 3). Tuberculosis is an exception to this general principle; recurrence is unusual after completion of a six-month regimen for most patients with drug-sensitive disease. For less severe infections, such as mucocutaneous candidiasis, mucocutaneous herpes simplex infection, or dermatomal herpes zoster, treatment of each recurrence is usually preferable to lifelong therapy unless the recurrences are very frequent or very severe. For secondary prophylaxis against some opportunistic infections, such as *M. avium* complex disease, the same dose schedule as for primary infection is usually recommended.^{75–77} For other infections, such as *P. carinii* pneumonia,⁴³ cytomegalovirus retinitis,^{78–83} cryptococcal meningitis,^{84–86} toxoplasmosis,^{87–89} histoplasmosis,^{90,91} and coccidioidomycosis,⁹² the regimen used for short-term therapy can be modified to provide a less intensive approach to long-term suppression, with good results.

DRUG INTERACTIONS

Each new medication added to a potentially complex drug regimen raises the chances of intolerance

TABLE 3. DRUG REGIMENS FOR SECONDARY PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS AFTER CHEMOTHERAPY FOR ACUTE INFECTION IN PATIENTS WITH HIV INFECTION.

PATHOGEN	FIRST CHOICE	ALTERNATIVES
<i>Pneumocystis carinii</i>	Trimethoprim-sulfamethoxazole, 1 double-strength tablet orally per day or 1 single-strength tablet orally per day	Trimethoprim-sulfamethoxazole, 1 double-strength tablet orally 3 times a week; dapsone, 50 mg orally twice a day or 100 mg orally once a day; dapsone, 50 mg orally per day, plus pyrimethamine, 50 mg orally once a week, plus leucovorin, 25 mg orally once a week; dapsone, 200 mg orally once a week, plus pyrimethamine, 75 mg orally once a week, plus leucovorin, 25 mg orally once a week; atovaquone, 1500 mg orally per day; aerosolized pentamidine, 300 mg monthly by Respigard II nebulizer
<i>Toxoplasma gondii</i>	Sulfadiazine, 500-1000 mg orally 4 times a day, plus pyrimethamine, 25-75 mg orally per day, plus leucovorin, 10 mg orally per day	Clindamycin, 300 mg orally 4 times a day or 450 mg orally 3 times a day, plus pyrimethamine, 25-75 mg orally per day, plus leucovorin, 10-25 mg orally per day
<i>Mycobacterium avium</i> complex	Clarithromycin, 500 mg orally twice a day, plus ethambutol, 15 mg/kg of body weight orally per day, with or without rifabutin, 300 mg orally per day	Azithromycin, 500 mg orally per day, plus ethambutol, 15 mg/kg orally per day, with or without rifabutin, 300 mg orally per day
Cytomegalovirus	Ganciclovir, 5-6 mg/kg intravenously 5-7 days a week or 1000 mg orally 3 times a day; foscarnet, 90-120 mg/kg intravenously per day; (for retinitis) ganciclovir sustained-release implant, every 6-9 mo, plus ganciclovir, 1000 to 1500 mg orally 3 times a day	Cidofovir, 5 mg/kg intravenously every other week; fomivirsen, 1 vial injected into the vitreous, then repeated every 2-4 wk; oral valganciclovir is currently investigational, but may prove useful
<i>Cryptococcus neoformans</i>	Fluconazole, 200 mg orally per day	Amphotericin B, 0.6-1.0 mg/kg intravenously 1-3 times a week; itraconazole, 200 mg orally per day
<i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i>	Itraconazole, 200 mg orally twice a day Fluconazole, 400 mg orally per day	Amphotericin B, 1.0 mg/kg intravenously once a week Amphotericin B, 1.0 mg/kg intravenously once a week; itraconazole, 200 mg orally twice a day
Salmonella species (not <i>S. typhi</i>) bacteremia	Ciprofloxacin, 500 mg orally twice a day for 6-8 mo	None
Herpes simplex virus	None; if recurrences are severe or frequent, consider acyclovir, 200 mg orally 3 times a day or 400 mg orally twice a day	Famciclovir, 500 mg orally twice a day; valacyclovir, 500 mg orally twice a day
Candida (oropharyngeal, esophageal, or vaginal)	None; if recurrences are severe or frequent, consider fluconazole, 100-200 mg orally per day	Itraconazole solution, 200 mg orally per day

or toxicity (Table 4). Possible pharmacokinetic interactions among antiinfective drugs must also be considered, especially for drugs that are metabolized by the hepatic cytochrome P-450 system. Particular attention should be directed toward the interactions of rifamycins (e.g., rifampin, rifabutin, and rifapentine), macrolides (especially clarithromycin), azoles (fluconazole and itraconazole), and antiretroviral protease inhibitors and nonnucleoside reverse-transcriptase inhibitors. Some important interactions are listed in Table 4 and are described in more detail elsewhere.⁶⁴

DISCONTINUING PROPHYLAXIS

Until recently, recommendations have emphasized the need to continue primary or secondary prophylaxis for life, given the irreversibility of HIV-induced immunodeficiency (Table 5). If the institution of highly active antiretroviral therapy restores CD4 cell counts to levels at which opportunistic infection rarely occurs, can primary or secondary prophylaxis be safely discontinued? This issue has been most extensively addressed in prospective studies assessing the discontinuation of primary prophylaxis against *P. carinii* pneumonia⁹³⁻⁹⁹ and *M. avium* complex disease^{96,100-102}

and of secondary prophylaxis against cytomegalovirus retinitis.^{78,97,103-106}

The risk associated with stopping primary prophylaxis against pneumocystis appears to be quite low among patients receiving highly active antiretroviral therapy whose CD4 cell counts have risen above 200 per cubic millimeter for three to six months (Table 6). In a Swiss study in which primary prophylaxis was stopped in 262 patients who had had CD4 cell counts of at least 200 per cubic millimeter and in whom at least 14 percent of all lymphocytes had been CD4 cells for at least 12 weeks, no cases of *P. carinii* pneumonia were diagnosed during a median follow-up period of 11 months (upper 95 percent confidence interval, 1.3 cases per 100 patient-years), nor did any cases of toxoplasma encephalitis occur in the 121 seropositive patients (upper 95 percent confidence interval, 2.7 cases per 100 patient-years).⁹⁴ These upper confidence limits were substantially lower than those in a historical control group with similar base-line characteristics (6.1 cases per 100 patient-years for *P. carinii* pneumonia and 15.9 cases per 100 patient-years for toxoplasmosis). Although most regimens for prophylaxis against *P. carinii* pneu-

TABLE 4. SELECTED PHARMACOKINETIC INTERACTIONS INVOLVING DRUGS USED TO PREVENT OPPORTUNISTIC INFECTIONS.

TARGETED PATHOGEN	PREVENTIVE DRUG	INTERACTING DRUG	EFFECT*	COMMENT
<i>Mycobacterium avium</i> complex	Clarithromycin	Ritonavir	Increase in plasma clarithromycin concentrations	No adjustment needed
		Nevirapine	Decrease in plasma clarithromycin AUC, but increase in AUC of active metabolite	No adjustment needed
		Astemizole, terfenadine, cisapride	Increase in plasma astemizole, terfenadine, or cisapride AUC, causing prolongation of QT interval	Avoid these combinations
	Rifabutin	Ritonavir, saquinavir, delavirdine	Substantial reduction in plasma concentrations of antiretroviral drugs and substantial increase in plasma rifabutin concentrations	Avoid these combinations
		Efavirenz	Substantial decrease in rifabutin AUC	Increase rifabutin to 450 mg daily
		Indinavir, nelfinavir, amprenavir	Reduction in plasma concentrations of antiretroviral drugs and increase in plasma rifabutin concentrations	Reduce rifabutin to 150 mg daily
<i>M. tuberculosis</i>	Rifampin	Fluconazole	Increase in plasma rifabutin concentrations	Monitor for toxic effects of rifabutin (especially uveitis)
		Indinavir, nelfinavir, saquinavir, ritonavir, amprenavir	Marked decrease in plasma protease-inhibitor concentrations	Avoid these combinations
Fungi	Fluconazole Itraconazole Ketoconazole	Delavirdine, nevirapine, efavirenz	Marked decrease in plasma antiretroviral-drug concentrations	Avoid these combinations
		Astemizole Terfenadine Cisapride	Increase in plasma astemizole, terfenadine, or cisapride AUC, causing prolongation of QT interval	Avoid these combinations

*AUC denotes area under the curve.

TABLE 5. RECOMMENDATION FOR INITIATING AND DISCONTINUING PRIMARY AND SECONDARY PROPHYLAXIS FOR ADULTS AND ADOLESCENTS WITH HIV INFECTION.*

PATHOGEN	PRIMARY PROPHYLAXIS			SECONDARY PROPHYLAXIS		
	START	STOP	RESTART	START	STOP	RESTART
<i>Pneumocystis carinii</i>	CD4 cell count <200/mm ³ or oropharyngeal candidiasis	CD4 cell count ≥200/mm ³ for 3–6 mo	Same as to start	Prior <i>P. carinii</i> pneumonia	CD4 cell count ≥200/mm ³ for 3–6 mo	Same as for primary prophylaxis
<i>Toxoplasma gondii</i>	CD4 cell count <100/mm ³ and IgG antibodies to toxoplasma	Follow <i>P. carinii</i> pneumonia guidelines, since all agents other than aerosol pentamidine will have some activity	Follow <i>P. carinii</i> pneumonia guidelines	Prior toxoplasmosis	Lifelong†	NA
<i>Mycobacterium tuberculosis</i>	Tuberculin skin test >5 mm (current or prior) and never treated, or contact with active case	NA	NA	Not indicated	NA	NA
<i>M. avium</i> complex	CD4 cell count <50/mm ³	CD4 cell count >100/mm ³ for 3–6 mo	Same as to start	Prior <i>M. avium</i> complex disease	Lifelong†	NA
Cytomegalovirus	Not recommended	NA	NA	Prior cytomegalovirus disease	CD4 cell count >100–150/mm ³ for 3–6 mo; non-sight-threatening lesion, adequate vision in other eye, and regular eye examination	CD4 cell count <50/mm ³
Herpes simplex virus, varicella-zoster virus, candida species, <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i> , <i>Coccidioides immitis</i>	Not recommended	NA	NA	Recommended only for prior cryptococcal, histoplasma, or coccidioides disease	Lifelong for cryptococcal, histoplasma, or coccidioides disease†	NA

*NA denotes not applicable.

†The data available are not sufficient to support a recommendation to stop secondary prophylaxis.

monia are simple, well tolerated, and inexpensive, there is a potentially substantial psychological benefit to patients who discontinue prophylaxis. Prophylaxis can, of course, be continued in patients who are reluctant to discontinue it, while a broader experience is accumulated to refine recommendations for discontinuation and reinitiation.

Preliminary reports of two ongoing prospective studies of more than 350 patients seropositive for antitoxoplasma antibodies suggest that primary antitoxoplasma prophylaxis can also be safely stopped after a response to highly active antiretroviral therapy.^{107,108} Usually, if primary prophylaxis against *P. carinii* pneumonia is discontinued, antitoxoplasma prophylaxis is stopped as well, because the same drug combination is used for both purposes.

According to observational data from the Adult/Adolescent Spectrum of HIV Disease cohort study (involving 767 patients), the Swiss HIV Cohort Study (involving 253 patients), and two prospective randomized trials (involving more than 1000 patients), primary prophylaxis against *M. avium* complex can be safely discontinued if the patient responds to highly active antiretroviral therapy with an increase in the CD4 cell count to more than 100 per cubic millimeter.^{96,100-102}

Clinicians have been more reluctant to stop secondary prophylaxis against opportunistic infections, given the demonstrated immunologic susceptibility of patients to these infections and the potentially

life-threatening consequences of recurrent infections. If cerebral toxoplasmosis, cytomegalovirus retinitis, cryptococcal meningitis, or disseminated histoplasmosis recurred, for instance, it might be difficult to reestablish control of the disease before irreversible damage or death occurred. Thus, there are more limited data available from ongoing studies about the safety of such an approach.¹⁰⁸⁻¹¹¹

For *P. carinii* pneumonia, stopping secondary prophylaxis appears to be safe.^{109,110} A combined analysis of eight prospective European cohort studies found no cases of recurrence after the discontinuation of secondary prophylaxis in patients with CD4 cell counts of more than 200 per cubic millimeter during 236 person-years of follow-up.

Currently available data (Table 7) suggest that in at least some patients treated with highly active antiretroviral therapy in whom CD4 cell counts have risen, long-term prophylactic regimens to suppress cytomegalovirus retinitis can be safely discontinued.^{78,97,103-106} Although the total number of patients studied is small, the fact that the almost invariable progression of cytomegalovirus retinitis previously occurred within a few months after therapy was stopped suggests that these results are credible.

Discontinuation of long-term maintenance therapy is reasonable after the resolution of lesions, but only if the CD4 cell count has been above 100 to 150 per cubic millimeter for at least three to six months, the lesions are not sight-threatening, vision is adequate in

TABLE 6. PROSPECTIVE STUDIES OF PATIENTS WITH HIV INFECTION WHO STOPPED PRIMARY PROPHYLAXIS AGAINST *PNEUMOCYSTIS CARINII*.

STUDY	ENTRY CRITERIA*	NO. OF PATIENTS	MEDIAN NADIR	MEDIAN CD4	MEDIAN FOLLOW-UP	NO. OF CASES OF <i>P. CARINII</i> PNEUMONIA
			CD4 CELL COUNT	CELL COUNT WHEN PROPHYLAXIS STOPPED		
			cells/mm ³		mo	
Schneider et al. ⁹³	CD4 cell count >200/mm ³ on 2 occasions ≥1 mo apart, on HAART	62	85†	353†	14.0†	0
Weverling et al. ⁹⁸	CD4 cell count >200/mm ³ , on HAART	236	147	312	5	0
Furrer et al. ⁹⁴	CD4 cell count ≥200/mm ³ and percentage ≥14% for at least 12 wk, on combination antiretroviral therapy	262	110	325	11.3	0
Lopez et al. ⁹⁵	CD4 cell count >200/mm ³ for more than 3 mo, on HAART; plasma HIV RNA <5000 copies/ml for more than 3 mo	274‡	102	340	11.3	0
Dworkin et al. ⁹⁶	CD4 cell count ≥200/mm ³ with increase of ≥100/mm ³ on antiretroviral therapy	736	150	330	9.2†	3
Kirk et al. ⁹⁷	CD4 cell count >200/mm ³ for more than 6 mo, on HAART	193	117	341	9.6	1

*HAART denotes highly active antiretroviral therapy.

†The mean rather than the median is given.

‡The number includes 24 patients who discontinued secondary prophylaxis.

TABLE 7. SELECTED STUDIES OF PATIENTS WITH HIV INFECTION WHO STOPPED SECONDARY PROPHYLAXIS AGAINST CYTOMEGALOVIRUS.

STUDY	ENTRY CRITERIA FOR CD4 CELL COUNT	NO. OF PATIENTS	MEDIAN CD4 CELL COUNT AT TIME OF CYTOMEGALOVIRUS RETINITIS	MEDIAN CD4 CELL COUNT WHEN PROPHYLAXIS STOPPED	MEDIAN FOLLOW-UP	NO. OF CASES OF CYTOMEGALOVIRUS
	cells/mm ³		cells/mm ³		mo	
Whitcup et al. ¹⁰³	>150	14	26	317	16.4*	0
Macdonald et al. ¹⁰⁴	Increase	11	42	183	5.2	0
Tural et al. ¹⁰⁵	>150†	7	35	Not stated	9	0
Vrabec et al. ¹⁰⁶	>100	8	<20	255*	11.4*	0
Kirk et al. ⁹⁷	>100	5	27	179	12	0

*The mean rather than the median is given.

†Additional criteria were a viral load of less than 200 copies per cubic millimeter and no cytomegalovirus detected by the polymerase chain reaction.

the contralateral eye, and the patient can be followed regularly by an ophthalmologist. Whether secondary prophylaxis can be safely discontinued for patients with extraocular cytomegalovirus disease is uncertain because of the paucity of reported cases.

Discontinuation of secondary cytomegalovirus prophylaxis according to these guidelines appears to be a reasonable approach. However, no approach to disease prevention can be expected to be risk-free. Cases have been documented in which cytomegalovirus retinitis (in contrast to immune recovery uveitis) recurred in patients whose CD4 cell counts increased to 300 per cubic millimeter during highly active antiretroviral therapy.¹¹² How often such cases occur needs to be carefully documented to determine whether this approach to the management of cytomegalovirus retinitis needs to be modified.

A concern about the interpretation of studies examining the discontinuation of prophylaxis is that the participating patients may not have been representative of all patients who fit the inclusion criteria; that is, clinicians may have elected not to enroll patients with weight loss, high plasma viral levels, or a history of multiple opportunistic infections.

If primary or secondary prophylaxis is stopped, when should it be restarted? It is reasonable to use the same criteria for restarting prophylaxis as for starting it initially, although there are no data specifically confirming the validity of such an approach. In patients with plasma HIV levels of more than 10,000 to 20,000 copies per milliliter, it may be prudent to reinstitute prophylaxis sooner. CD4 cell counts and plasma viral load should be measured every three to six months, with an increase in monitoring frequency as the CD4 cell count declines.

CONCLUSIONS

Specific antimicrobial prophylaxis, by itself or in conjunction with antiretroviral therapy, can reduce

the substantial morbidity and mortality caused by opportunistic infections in patients with HIV infection. We are in a fortunate period in which the effects of opportunistic infections can be dramatically decreased for patients with access to comprehensive care in whom durable immune reconstitution is induced by highly active antiretroviral therapy. It is clear that prophylaxis can be safely discontinued in selected patients with immune reconstitution induced by antiretroviral agents. Understanding and applying measures to prevent opportunistic infections has had, and will continue to have, a critical role in the treatment of patients with HIV infection.

REFERENCES

1. *Pneumocystis pneumonia* — Los Angeles. MMWR Morb Mortal Wkly Rep 1981;30:250-2.
2. Gottlieb MS, Schroff R, Schanker HM, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981;305:1425-31.
3. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med 1981;305:1431-8.
4. Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals manifested by chronic perianal ulcerative herpes simplex lesions. N Engl J Med 1981;305:1439-44.
5. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.
6. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992–1997. MMWR CDC Surveill Summ 1999;48(SS-2):1-22.
7. Miller V, Staszewski S, Nisius G, Lepri AC, Sabin C, Phillips AN. Risk of new AIDS diseases in people on triple therapy. Lancet 1999;353:463-4.
8. Ledergerber B, Egger M, Opravil MR, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study: Swiss HIV Cohort Study. Lancet 1999;353:863-8.
9. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). MMWR Morb Mortal Wkly Rep 1999;48(RR-10):1-66.
10. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep 1992;41(RR-17):4-19.

11. Moore RD, Keruly JC, Chaisson RE. Decline in CMV and other opportunistic disease with combination antiretroviral therapy. In: Proceedings of the Fifth Conference on Retroviruses and Opportunistic Infections, Chicago, February 1-5, 1998:113. abstract.
12. Costagliola D. Clinical manifestations of HIV infections in the era of highly active antiretroviral treatment (HAART) in France. In: Abstracts of the 12th International Conference on AIDS, Geneva, June 28-July 3, 1998:82. abstract.
13. Grulich AE. AIDS-associated non-Hodgkin's lymphoma in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 1999;21:Suppl 1:S27-S30.
14. Lundgren JD, Johnson A, Pradier C, et al. The changing spectrum of AIDS across Europe: 1994-1999: the EuroSIDA study. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 26-29, 1999. Washington, D.C.: American Society for Microbiology, 1999:91. abstract.
15. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep* 1997;46(RR-12):1-46.
16. 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.
17. Masur H, Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium* Complex. Recommendations on prophylaxis and therapy for disseminated *Mycobacterium avium* complex disease in patients infected with the human immunodeficiency virus. *N Engl J Med* 1993;329:898-904.
18. Giorgi J, Majchrowicz MA, Johnson TD, Hultin P, Matud J, Detels R. Immunologic effects of combined protease inhibitor and reverse transcriptase inhibitor therapy in previously treated chronic HIV-1 infection. *AIDS* 1998;12:1833-44.
19. Engels EA, Rosenberg PS, O'Brien TR, Goedert JJ. Plasma HIV viral load in patients with hemophilia and late-stage HIV disease: a measure of current immune suppression: Multicenter Hemophilia Cohort Study. *Ann Intern Med* 1999;131:256-64.
20. Kaplan JE, Hanson DL, Dworkin MS, Jones JL. HIV plasma RNA, an independent predictor of opportunistic infections in HIV-infected persons. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 26-29, 1999. Washington, D.C.: American Society for Microbiology, 1999:13. abstract.
21. Immunological markers in HIV-infected pregnant women. *AIDS* 1997;11:1859-65.
22. 1995 Revised guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep* 1995;44(RR-4):1-11.
23. Zurlo JJ, Wood L, Gaglione MM, Polis MA. Effect of splenectomy on T lymphocyte subsets in patients infected with the human immunodeficiency virus. *Clin Infect Dis* 1995;20:768-71.
24. Phair J, Muñoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men with human immunodeficiency virus type 1. *N Engl J Med* 1990;322:161-5.
25. Miller V, Mocroft A, Reiss P, et al. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: results from the EuroSIDA study. *Ann Intern Med* 1999;130:570-7.
26. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *MMWR Morb Mortal Wkly Rep* 1998;47(RR-20):1-58.
27. Richards FO Jr, Kovacs JA, Luft BJ. Preventing toxoplasmic encephalitis in persons infected with human immunodeficiency virus. *Clin Infect Dis* 1995;21:Suppl 1:S49-S56.
28. Stewart JA, Reef SE, Pellett PE, Corey L, Whitley RJ. Herpesvirus infections in persons infected with human immunodeficiency virus. *Clin Infect Dis* 1995;21:Suppl 1:S114-S120.
29. Keely SP, Stringer JR. Sequences of *Pneumocystis carinii* f. sp. hominis strains associated with recurrent pneumonia vary at multiple loci. *J Clin Microbiol* 1997;35:2745-7.
30. Tsolaki AG, Miller RE, Underwood AP, Banerji S, Wakefield AE. Genetic diversity at the internal transcribed spacer regions of the rRNA operon among isolates of *Pneumocystis carinii* from AIDS patients with recurrent pneumonia. *J Infect Dis* 1996;174:141-56.
31. USPHS/IDSA Prevention of Opportunistic Infections Working Group. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. *Clin Infect Dis* 1995;21:Suppl 1:S32-S43.
32. Ward JW, Hanson DL, Jones J, Kaplan J. Pneumococcal vaccination and the incidence of pneumonia among HIV-infected persons. In: Program and abstracts of the 34th Annual Meeting of the Infectious Diseases Society of America, New Orleans, September 18-20, 1996:81. abstract.
33. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1997;46(RR-8):1-24.
34. Nielsen H, Kvinesdal B, Benfield T, Lundgren JD, Konradsen HB. Rapid loss of specific antibodies after pneumococcal vaccination in patients with human immunodeficiency virus-1 infection. *Scand J Infect Dis* 1998;30:597-601.
35. Fleming C, Cilento J, Steger K, McNamara E, Pelton S, Craven D. Immunogenicity of revaccination with pneumococcal vaccine in HIV-infected patients on combination antiretroviral therapy. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30-February 2, 2000:123. abstract.
36. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998;338:286-90.
37. Tasker SA, Treanor JJ, Paxton WB, Wallace MR. Efficacy of influenza vaccination in HIV-infected persons: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999;131:430-3.
38. Lundgren JD, Barton SE, Lazzarin A, et al. Factors associated with the development of *Pneumocystis carinii* pneumonia in 5,025 European patients with AIDS. *Clin Infect Dis* 1995;21:106-13.
39. Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. *J Infect Dis* 1998;178:1126-32.
40. Bazzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995;332:693-9.
41. Schneider MME, Hoepelman AIM, Eeftink Schattenkerk JKM, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. *N Engl J Med* 1992;327:1836-41.
42. Schneider MME, Nielsen TL, Nelsing S, et al. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus. *J Infect Dis* 1995;171:1632-6.
43. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome: AIDS Clinical Trials Group protocol 021. *N Engl J Med* 1992;327:1842-8.
44. El-Sadr W, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected persons: Terry Bein Community Programs for Clinical Research on AIDS. *Clin Infect Dis* 1999;29:775-83.
45. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1992;117:106-11.
46. Para MF, Dohn M, Frame P, et al. ACTG 268 Trial — gradual initiation of trimethoprim/sulfamethoxazole (T/S) as primary prophylaxis for *Pneumocystis carinii* pneumonia (PCP). In: Proceedings of the Fourth Conference on Retroviruses and Opportunistic Infections, Washington, D.C., January 22-26, 1997:65. abstract.
47. Leoung G, Stanford J, Giordano M, et al. A randomized, double-blind trial of TMP/SMX dose escalation vs. direct rechallenge in HIV+ persons at risk for PCP and with prior treatment-limiting rash or fever. In: Addendum to Program and abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, September 28-October 1, 1997. Washington, D.C.: American Society for Microbiology, 1997. abstract.
48. Podzamczar D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of *Pneumocystis pneumonia* and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995;122:755-61.
49. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1995;20:531-41.
50. Girard P-M, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993;328:1514-20.
51. Pearson RD, Hewlett EL. Pentamidine for the treatment of *Pneumocystis carinii* pneumonia and other protozoal diseases. *Ann Intern Med* 1985;103:782-6.
52. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared

- with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998;339:1889-95.
53. Ma L, Borio L, Masur H, Kovacs JA. *Pneumocystis carinii* dihydropteroate synthase but not dihydrofolate reductase gene mutations correlate with prior trimethoprim-sulfamethoxazole or dapsone use. *J Infect Dis* 1999;180:1969-78.
54. Helweg-Larsen J, Benfield TL, Eugen-Olsen J, Lundgren JD, Lundgren B. Effects of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of AIDS-associated *P. carinii* pneumonia. *Lancet* 1999;354:1347-51.
55. Kazanjian P, Armstrong W, Hossler PA, et al. *Pneumocystis carinii* mutations are associated with duration of sulfa prophylaxis and with sulfa treatment failure in AIDS patients. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:119. abstract.
56. Halsey NA, Coberly JS, Desormeaux J, et al. Randomized trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet* 1998;351:786-92.
57. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med* 1997;337:801-8.
58. Mwinga AG, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS* 1998;12:2447-57.
59. Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. *AIDS* 1997;11:875-82.
60. Gordin FM, Matts JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. *N Engl J Med* 1997;337:315-20.
61. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs. isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial: Terry Bein Community Programs for Clinical Research on AIDS. *JAMA* 2000;283:1445-50.
62. Graham NMH, Galai N, Nelson KE, et al. Effect of isoniazid chemoprophylaxis on HIV-related mycobacterial disease. *Arch Intern Med* 1996;156:889-94.
63. The USPHS Rifapentine Trial Group, Vernon A, Khan A, Bozeman L, Wang YC. Update on US Public Health Service (USPHS) Study 22: a trial of once weekly isoniazid (INH) & rifapentine (RPT) in the continuation phase of TB treatment. *Am J Respir Crit Care Med* 1998;157:Suppl: A467. abstract.
64. Flexner C, Piscitelli SC. Drug administration and interactions. In: Dolin R, Masur H, Saag MS, eds. *AIDS therapy*. New York: Churchill Livingstone, 1999:785-97.
65. Benson CA, Cohn DL, Williams P, ACTG 196/CPCRA 009 Study Team. A phase III prospective, randomized, double-blind study of the safety and efficacy of clarithromycin (CLA) vs. rifabutin (RBT) vs. CLA+RBT for prevention of *Mycobacterium avium* complex (MAC) disease in HIV+ patients with CD4 counts ≤ 100 cells/ μ L. In: Proceedings of the Third Conference on Retroviruses and Opportunistic Infections, Washington, D.C., January 28–February 1, 1996:91. abstract.
66. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. *N Engl J Med* 1996;335:384-91.
67. Havlir DV, Dubé MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. *N Engl J Med* 1996;335:392-8.
68. Dunne MW, Bozzette S, McCutchan JA, et al. Efficacy of azithromycin in prevention of *Pneumocystis carinii* pneumonia: a randomized trial. *Lancet* 1999;354:891-5.
69. Spector SA, McKinley GF, Lalezari JP, et al. Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. *N Engl J Med* 1996;334:1491-7.
70. Brosgart CL, Louis TA, Hillman DW, et al. A randomized, placebo-controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of cytomegalovirus disease in HIV-infected individuals: Terry Bein Community Programs for Clinical Research on AIDS. *AIDS* 1998;12:269-77.
71. Powderly WG, Finkelstein DM, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995;332:700-5.
72. Schuman P, Capps L, Peng G, et al. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997;126:689-96.
73. Havlir DV, Dube MP, McCutchan JA, et al. Prophylaxis with weekly versus daily fluconazole for fungal infections in patients with AIDS. *Clin Infect Dis* 1998;27:1369-75.
74. McKinley DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis against fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. *Clin Infect Dis* 1999;28:1049-56.
75. Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex. *Clin Infect Dis* 1999;28:1080-5.
76. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *Mycobacterium avium* complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. *Clin Infect Dis* 1999;29:125-33.
77. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *N Engl J Med* 1996;335:377-83.
78. Martin DE, Kuppermann BD, Wolitz RA, et al. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med* 1999;340:1063-70.
79. Studies of the Ocular Complications of AIDS (SOCA), AIDS Clinical Trials Group. Cytomegalovirus (CMV) culture results, drug resistance, and clinical outcome in patients with AIDS and CMV retinitis treated with foscarnet or ganciclovir. *J Infect Dis* 1997;176:50-8.
80. Martin D, Sierra-Madero J, Walmsley S, Wolitz R, Brown F, Robinson C. Valganciclovir (VGCV) vs. IV ganciclovir (GCV) as induction therapy for newly diagnosed cytomegalovirus (CMV) retinitis: a randomized, controlled study. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:119. abstract.
81. Palestine AG, Polis MA, De Smet MD, et al. A randomized, controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS. *Ann Intern Med* 1991;115:665-73.
82. Studies of Ocular Complications of AIDS Research Group, AIDS Clinical Trials Group. Parenteral cidofovir for cytomegalovirus retinitis in patients with AIDS: the HPMPIC Peripheral Cytomegalovirus Retinitis Trial: a randomized, controlled trial. *Ann Intern Med* 1997;126:264-74.
83. Drew WL, Ives D, Lalezari JP, et al. Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. *N Engl J Med* 1995;333:615-20.
84. Bozzette SA, Larsen RA, Chiu J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. *N Engl J Med* 1991;324:580-4.
85. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992;326:793-8.
86. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy of AIDS-associated cryptococcal meningitis. *Clin Infect Dis* 1999;28:291-6.
87. Podzameczer D, Miro JM, Bolao F, et al. Twice-weekly maintenance therapy with sulfadiazine-pyrimethamine to prevent recurrent toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1995;123:175-80.
88. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS: a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992;116:33-43.
89. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996;22:268-75.
90. Wheat J. Histoplasmosis. In: Dolin R, Masur H, Saag MS, eds. *AIDS therapy*. New York: Churchill Livingstone, 1999:412-22.
91. Wheat J, Hafner R, Wulfsohn M, et al. Prevention of relapse of histoplasmosis with itraconazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1993;118:610-6.
92. Ampel NM. Coccidioidomycosis. In: Dolin R, Masur H, Saag MS, eds. *AIDS therapy*. New York: Churchill Livingstone, 1999:423-32.
93. Schneider MME, Borleffs JCC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet* 1999;353:201-3.
94. Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. *N Engl J Med* 1999;340:1301-6.

- 95.** Lopez JC, Miro JM, Pena JM, Podzamcz D. Discontinuation of PCP prophylaxis is safe in HIV-infected patients after immunological recovery with HAART: results of the Gesida 04/98 study. In: Addendum to Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 26–29, 1999. Washington, D.C.: American Society for Microbiology, 1999:19. abstract.
- 96.** Dworkin M, Hanson D, Jones J, Kaplan J, Adult/Adolescent Spectrum of HIV Disease Project (ASD). The risk for *Pneumocystis carinii* pneumonia (PCP) and disseminated nontuberculous mycobacteriosis (dMb) after an antiretroviral therapy (ART) associated increase in the CD4+ T-lymphocyte count. In: Proceedings of the Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, January 31–February 4, 1999:198. abstract.
- 97.** Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? AIDS 1999;13:1647-51.
- 98.** Weverling GJ, Mocroft A, Ledergerber B, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. Lancet 1999;353:1293-8.
- 99.** Yangco BG, Von Bargen JC, Moorman AC, Holmberg SD. Discontinuation of chemoprophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection. Ann Intern Med 2000;132:201-5.
- 100.** Currier JS, Williams PL, Koletar S, et al. A randomized, placebo-controlled trial of azithromycin prophylaxis for the prevention of mycobacterium avium complex (MAC) in subjects with increases in CD4 cells on antiretroviral therapy. In: Addendum to Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 26–29, 1999. Washington, D.C.: American Society for Microbiology, 1999:19. abstract.
- 101.** Furrer H, Talenti A, Rossi M, Ledergerber B. Discontinuing or withholding primary prophylaxis against *M. avium* in patients on successful antiretroviral combination therapy: the Swiss HIV Cohort experience. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:122. abstract.
- 102.** El-Sadr WM, Burman W, Grant L, et al. Prophylaxis for *Mycobacterium avium* complex can be deferred among patients with a past CD4 count <50 cells/mm³ who responded to antiretroviral therapy: results of a placebo-controlled trial (CPCRA 048). In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:122. abstract.
- 103.** Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anti-cytomegalovirus therapy in persons with HIV infection and cytomegalovirus retinitis. JAMA 1999;282:1633-7.
- 104.** Macdonald JC, Torriani FJ, Morse LS, Karavellas MP, Reed JB, Freeman WR. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. J Infect Dis 1998;177:1182-7.
- 105.** Tural C, Romeu J, Sirena G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. J Infect Dis 1998;177:1080-3.
- 106.** Vrabec TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. Ophthalmology 1998;105:1259-64.
- 107.** Furrer H, Opravil M, Rossi M, et al. The Swiss StopCox Study: is it safe to discontinue PCP prophylaxis in patients with detectable viremia, low nadir CD4 count or *T. gondii* seropositivity? In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:122. abstract.
- 108.** Miro JM, Lopez JC, Podzamcz D, et al. Discontinuation of toxoplasmic encephalitis prophylaxis is safe in HIV-1 and *T. gondii* co-infected patients after immunological recovery with HAART: preliminary results of the GESIDA 04/98-B Study. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:119. abstract.
- 109.** Ledergerber B, Mocroft A, Reiss P, et al. It is safe to discontinue secondary prophylaxis for PCP in HIV-infected patients treated with HAART: results from eight prospective European cohorts. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:235. abstract.
- 110.** Koletar SL, Heald AE, Murphy RL, et al. Discontinuing primary and secondary PCP prophylaxis in patients who have increased CD4 counts in response to antiretroviral therapy: preliminary results — ACTG 888. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:122. abstract.
- 111.** Aberg JA, Price RW, Heeren DM, Pearce RB, Bredt B. Discontinuation of antifungal therapy for cryptococcosis after immunologic response to antiretroviral therapy. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:123. abstract.
- 112.** Johnson S, Benson C, Johnson D, Weinberg A. Recurrent cytomegalovirus (CMV) retinitis in a patient on highly active antiretroviral therapy (HAART) despite apparent immune reconstitution. In: Proceedings of the Seventh Conference on Retroviruses and Opportunistic Infections, San Francisco, January 30–February 2, 2000:127. abstract.

CORRECTION

Prophylaxis against Opportunistic Infections in Patients with Human Immunodeficiency Virus Infection

Prophylaxis against Opportunistic Infections in Patients with Human Immunodeficiency Virus Infection . On page 1421, beginning on the first line of the right-hand column, the dose of the double-strength tablet should have read, "160 mg of trimethoprim plus 800 mg of sulfamethoxazole," not "80 mg of trimethoprim plus 400 mg of sulfamethoxazole," as printed, and the dose of the single-strength tablet should have read, "80 mg of trimethoprim plus 400 mg of sulfamethoxazole," not "40 mg of trimethoprim plus 200 mg of sulfamethoxazole," as printed. Also, in Table 2, next to the entry "Isoniazid-resistant source case (if known)," the first-choice regimen should have read, "Rifampin, 600 mg orally per day, plus pyrazinamide, 20 mg/kg orally per day, for 2 mo," not "pyrazinamide, 200 mg/kg," as printed. We regret the error.