Prophylaxis of opportunistic infections in persons with HIV infection

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■ **BACKGROUND** Morbidity and mortality associated with human immunodeficiency virus infection and the acquired immunodeficiency syndrome is most often related to associated opportunistic infections.

■ **OBJECTIVE** To review the prophylaxis of common opportunistic infections in patients with human immunodeficiency virus.

■ **SUMMARY** Prophylactic treatment for *Pneumocystis carinii* pneumonia should begin when the CD4 count falls below 200 cells per μL. Recommended treatment consists of trimethoprim 160 mg and sulfamethoxazole 800 mg daily, but other regimens have been successfully used. This regimen appears to also prevent the development of toxoplasmic encephalitis. Fluconazole 100 mg once or twice weekly can prevent oral and esophageal candidiasis, but its efficacy against life-threatening fungal infections is unproved. Rifabutin 300 mg daily can delay the development of disseminated *Mycobacterium avium* complex infection. Daily therapy with 300 mg of isoniazid for at least 9 months is recommended for persons at risk for tuberculosis.

■ **CONCLUSIONS** Prevention of opportunistic infections can prolong the lives of persons infected with human immunodeficiency virus. Effective regimens are available for preventing some of these infections, and studies are in progress to establish optimum regimens for others.

■ INDEX TERMS: OPPORTUNISTIC INFECTIONS; HIV INFECTIONS
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THE UNUSUAL bacterial, viral, parasitic, and fungal infections that occur in patients infected with human immunodeficiency virus (HIV) result from the progressive decline in immune function caused by HIV. The number of circulating $CD4^+$ lymphocytes is strongly and inversely associated with the degree of immune deficiency, and the common opportunistic infections associated with HIV infection occur at threshold levels of CD4 depletion: more virulent pathogens (eg, *Mycobacterium tuberculosis*) appear at earlier stages of immunodeficiency, and less virulent pathogens (eg, *Pneumocystis carinii*, *Mycobacterium avium* complex, cytomegalovirus) appear later.

A retrospective study conducted in Australia correlated the development of HIV-associated infections with CD4 levels. CD4 counts were drawn from 2 months before to 1 month after infections appeared in 222 outpatients between 1983 and 1989. Individuals with fewer than 500 CD4 cells per μL were generally asymptomatic. Oropharyngeal candidiasis or tuberculosis developed in patients with between 250 and 500 cells per μL, Kaposi's sarcoma occurred in patients with between 150 and 200 cells per μL, and infections with *P*

TABLE
RECOMMENDED PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS

Disease	CD4 count threshold	Recommended prophylaxis	Alternative agents
Pneumocystis carinii pneumonia	200 cells per μL or 15%	Trimethoprim 160 mg and sulfamethoxazole 800 mg three to seven times a week	Aerosolized pentamidine 300 mg monthly Dapsone 100 mg three times a week or 50 mg daily, with or without trimethoprim or pyrimethamine Possibly effective: atovaquone, clindamycin with primaquine
Toxoplasmosis	Not determined	Trimethoprim 160 mg and sulfamethoxazole 800 mg three to seven times a week	Possibly effective: dapsone 100 mg every other day with pyrimethamine
Fungal infections	Not determined	Fluconazole 100 mg once or twice a week (routine use is not established)	Possibly effective: ketoconazole
Disseminated *Mycobacterium avium complex*	100 cells per μL	Rifabutin 300 mg daily	Possibly effective: clarithromycin, *azithromycin*
Mycobacterium tuberculosis infection	Any (for persons with >5-mm induration on purified protein derivative test)	Isoniazid 300 mg daily for at least 9 months	

carinii, *Toxoplasma gondii*, M *avium* complex, herpes simplex virus, *Candida* species, and *Cryptococcus neoformans* developed in patients with fewer than 100 CD4 cells per μL. Cytomegalovirus disease, predominantly retinitis, did not occur until the CD4 count fell below 50 cells per μL.[1]

Attempts have been made to formulate effective and timely strategies to prevent the most common opportunistic infections affecting HIV-infected patients. Highly effective prophylactic regimens exist for some pathogens, popular but unproved regimens exist for other organisms, and other regimens are still undergoing large clinical trials. For some organisms, no effective regimens have yet been devised. Current recommendations are summarized in the *Table*.

PNEUMOCYSTIS CARINII PNEUMONIA

The therapeutic intervention with the greatest impact on survival for patients with HIV has probably been the widespread introduction of routine prophylaxis against *P carinii* pneumonia (PCP). Early in the epidemic, 80% of North American AIDS patients would experience at least one episode of PCP. As prophylaxis for PCP has become the standard of care, the incidence of PCP has fallen considerably.

Prophylaxis is recommended when the CD4 level falls below 200 cells per μL, although some practitioners start at 250 cells per μL. Additionally, patients with oral thrush or with unexplained fever (oral temperature > 100°F) for longer than 2 weeks should also consider prophylaxis for PCP.[2] Many practitioners base the decision to start prophylaxis on the percentage of lymphocytes bearing the CD4 marker (CD4%) instead of on the number of CD4 cells because the CD4% is directly measured and is less subject to variation with repeated measurements. In most individuals, a CD4% of 14% to 15% is equivalent to approximately 200 CD4 cells per μL.[3]

Trimethoprim-sulfamethoxazole

A regimen of trimethoprim and sulfamethoxazole is the treatment of choice for preventing PCP. In the first prophylactic study, 60 patients with preexisting Kaposi's sarcoma were randomly assigned to take trimethoprim 160 mg and sulfamethoxazole 800 mg twice daily or placebo. Sixteen episodes of PCP occurred in 30 patients receiving placebo, while no episodes of PCP occurred in 30 patients taking trimethoprim and sulfamethoxazole.[4] However, the incidence of side effects in the active-treatment group was high: half had some toxicity, and five of

30 patients were removed from the study because of side effects.

A retrospective study evaluated a lower dosage of these agents (trimethoprim 160 mg and sulfamethoxazole 800 mg every other day) in 67 patients. Only one episode of PCP occurred in the 35 patients who had already had PCP (the secondary-prophylaxis group), and no episodes of PCP occurred in the 32 patients who had never had PCP (the primary-prophylaxis group).[5] Although patients had to be able to tolerate these agents to enter the study, side effects still occurred in 52% of the patients who had already had PCP and in 31% of those who had not. These consisted mostly of rashes, pruritus, and nausea.

Another retrospective study described 116 patients who received trimethoprim 160 mg and sulfamethoxazole 800 mg every Monday, Wednesday, and Friday. Seventy-one had previous episodes of PCP, and 45 had fewer than 200 CD4 cells per μL but no previous PCP. There were no episodes of PCP in either group after a mean of 18.5 months in the secondary-prophylaxis group and 24.2 months in the primary-prophylaxis group. Twenty-eight percent of the patients had adverse reactions, and 13% permanently stopped their medication.[6] This study was the first to suggest that these agents may also prevent *T gondii* infection.

Aerosolized pentamidine

Though it was the first agent shown to effectively prevent PCP, aerosolized pentamidine is clearly a second-line alternative. An elegant, large-scale community trial conducted by a consortium of physicians in the San Francisco area followed 408 patients who took three different regimens of aerosolized pentamidine. Those receiving higher doses (150 mg every other week or 300 mg monthly) had a significantly lower incidence of PCP than those receiving 30 mg every other week.[7]

Another study followed 51 patients with a history of PCP. Within an average of 10 months, 9% of patients treated with aerosolized pentamidine acquired PCP again. In contrast, within an average of 8.7 months, 61% of untreated patients acquired PCP.[8] Another primary prophylactic study of 223 patients resulted in an incidence of PCP of 27.1% per year in patients who received placebo and 8.6% per year in patients who received aerosolized pentamidine.[9] Finally, a study of aerosolized pentamidine for secondary prophylaxis of PCP in 162 patients resulted in a 9% relapse rate at 24 weeks in the aerosolized-pentamidine group vs 50% in the placebo group.[10]

In a recent comparative trial of primary prophylaxis, 215 patients with fewer than 200 CD4 cells per μL were randomized to receive either monthly aerosolized pentamidine, trimethoprim 80 mg and sulfamethoxazole 400 mg daily, or trimethoprim 160 mg and sulfamethoxazole 800 mg daily. There were six episodes of PCP among 71 patients in the aerosolized-pentamidine group (11%) and no episodes among the 142 patients in either of the trimethoprim-and-sulfamethoxazole groups.[11] Thirty-five patients taking trimethoprim and sulfamethoxazole experienced side effects necessitating withdrawal from the study, whereas only two patients in the aerosolized-pentamidine group did. A similar study of 310 patients with previous PCP resulted in 14 episodes of PCP in 154 patients (9.1%) taking trimethoprim 160 mg and sulfamethoxazole 800 mg daily vs 36 episodes of PCP in 156 patients (23.1%) receiving monthly aerosolized pentamidine.[12]

Aerosolized pentamidine is probably not appropriate for patients with previous pulmonary disease, because drug delivery may be erratic with altered pulmonary architecture. Also of concern is the increased incidence of atypical PCP on chest radiography, with upper-lobe disease and pneumothorax more commonly occurring in patients treated with aerosolized pentamidine.[13] The diagnosis of PCP may be more difficult in these patients than in patients not receiving aerosolized pentamidine because cytologic study of induced sputum or bronchoalveolar washings is often negative, necessitating transbronchial biopsy or multilobar lavage.[13] Finally, extrapulmonary *P carinii* infection, with an incidence of fewer than 1% of cases of PCP, occurs primarily in patients treated with aerosolized pentamidine, because there is little systemic absorption of the medication from the lung.[14]

Dapsone

Dapsone, with its long serum half-life (21 to 44 hours) and low cost, has emerged as a promising alternative to trimethoprim and sulfamethoxazole. An early study of 16 patients with fewer than 200 CD4 cells per μL who took dapsone 100 mg weekly and of 46 historical controls not receiving prophylaxis resulted in 16 episodes of PCP in the control arm and one episode of PCP in the dapsone arm.[15]

Another study using low doses of dapsone fol-

lowed 61 patients both with and without previous PCP for a mean of 9 months. One episode of PCP occurred in the 50 patients given dapsone 200 mg weekly, while no episodes of PCP occurred in the groups given dapsone 100 mg weekly (seven patients) or 300 mg weekly (four patients). Adverse reactions, most commonly rash and anemia, occurred in eight patients (13%).[16]

Finally, one study combined dapsone 100 mg twice a week with pyrimethamine 25 mg twice a week and followed 109 patients for a mean of 15 months (range 8 to 18 months). Only one episode of PCP occurred among 20 patients with previous PCP, and one episode occurred among 89 patients without previous PCP. Pruritus or rash developed in five patients. In the 54 patients with a positive serologic test for *T gondii*, there were no episodes of toxoplasmosis in the central nervous system during the period of the study.[17]

Two recent studies reported higher-than-expected rates of PCP in patients treated with dapsone. In 142 patients taking dapsone 100 mg with pyrimethamine 25 mg three times weekly, there were 17 episodes of PCP (12%) vs two episodes of PCP in 84 patients (2%) taking trimethoprim 160 mg and sulfamethoxazole 800 mg three times weekly.[18] A second study followed 68 patients receiving monthly aerosolized pentamidine, 66 patients taking trimethoprim 160 mg and sulfamethoxazole 800 mg every other day, and 63 patients taking dapsone 100 mg with pyrimethamine 25 mg twice weekly. There were nine episodes of PCP in the dapsone group, four in the aerosolized-pentamidine group, and one in the trimethoprim-and-sulfamethoxazole group.[19]

In an 18-month study of 50 patients given dapsone 100 mg twice a week and 46 patients given monthly aerosolized pentamidine, there were nine episodes of PCP in the dapsone group and eight in the aerosolized-pentamidine group. Two episodes of central nervous system toxoplasmosis were reported in each group.[20] Among 331 patients given trimethoprim 160 mg and sulfamethoxazole 800 mg three times a week, dapsone 100 mg with pyrimethamine 25 mg weekly, or monthly aerosolized pentamidine, the incidence of PCP was not significantly different among groups (3% per year for trimethoprim and sulfamethoxazole, 8.3% for dapsone with pyrimethamine, and 5.6% for aerosolized pentamidine). Side effects were much more common in the trimethoprim-and-sulfamethoxazole group (10 patients) and in the dapsone-and-pyrimethamine group (nine patients) than in the aerosolized-pentamidine group (one patient).[21]

Most recently, a trial compared dapsone and pyrimethamine with aerosolized pentamidine as primary prophylaxis against both PCP and toxoplasmosis. The incidence rates of PCP were identical, with 10 cases of PCP among the 176 patients treated with monthly aerosolized pentamidine and 10 cases of PCP among the 173 patients treated with dapsone 50 mg and pyrimethamine 50 mg weekly. However, 32 cases of toxoplasmosis occurred in the aerosolized-pentamidine group, compared with 19 in the dapsone-and-pyrimethamine group. More patients had to discontinue therapy with dapsone and pyrimethamine because of side effects (42 patients) than did patients receiving aerosolized pentamidine (three patients).[22] Patients receiving dapsone for prolonged periods may need prescreening for glucose-6-phosphate dehydrogenase (G6PD) deficiency. However, in general, significant hemolysis does not occur in persons with G6PD deficiency who receive 50 mg per day or less of dapsone.

Allergic reactions have been reported in 8% to 54% of patients treated with prophylactic or therapeutic doses of trimethoprim and sulfamethoxazole. One study, in 31 patients with previous non-life-threatening reactions to trimethoprim and sulfamethoxazole who were rechallenged first with trimethoprim alone, resulted in five patients acquiring rashes, which were serious enough to necessitate stopping trimethoprim in two patients. The remaining 26 patients underwent treatment with trimethoprim and sulfamethoxazole; 15 (58%) had hypersensitivity reactions, which were severe enough to necessitate stopping trimethoprim and sulfamethoxazole in 12. Finally, nine patients with reactions to trimethoprim and sulfamethoxazole were switched to dapsone, resulting in two additional rashes, one of which necessitated discontinuing dapsone. The authors concluded that rechallenge was more likely to be successful in groups with lower CD4 counts. Trimethoprim alone was responsible for hypersensitivity in 16% of patients, and cross-reactivity between dapsone and trimethoprim and sulfamethoxazole was low.[23]

Sulfadoxine and pyrimethamine

The combination of sulfadoxine and pyrimethamine has also been tried for PCP prophylaxis. In one study, 30 patients with Kaposi's sarcoma took sulfadoxine and pyrimethamine once a week

and had seven episodes of PCP after a mean of 6 months. Ten patients (33%) experienced side effects, with fatigue, nausea, erythroderma, fevers, and anemia most common.[24] In another study, 33 patients with previous PCP had no recurrences of PCP when they used sulfadoxine and pyrimethamine weekly for a mean of 27 weeks. However, five patients had to stop because of adverse reactions.[25] In general, the toxicities of sulfadoxine and pyrimethamine militate against their routine use in PCP prophylaxis.

Other agents with known activity against *P carinii*, but that have not yet undergone or completed clinical trials for prophylaxis, include atovaquone and the combination of clindamycin and primaquine. Though atovaquone has fewer adverse effects than trimethoprim and sulfamethoxazole, it is somewhat less effective, and its use as a prophylactic agent should be approached with caution because of its erratic bioavailability.[26]

Recommendations for preventing PCP

The US Public Health Service Task Force on PCP Prophylaxis recommends giving trimethoprim 160 mg and sulfamethoxazole 800 mg twice a day, 7 days a week for primary prophylaxis or once a day for secondary prophylaxis.[2] However, given the success of lower dosages in the quoted studies, it appears reasonable to give trimethoprim 160 mg and sulfamethoxazole 800 mg either every other day or three times a week for both primary and secondary prophylaxis. Patients who cannot tolerate trimethoprim and sulfamethoxazole should receive 300 mg of aerosolized pentamidine monthly by Respirgard II jet nebulizer (Marquest, Englewood, Colo) or 60 mg every 2 weeks after a loading regimen of five doses of 60 mg over a 2-week period by Fisons nebulizer (Rochester, NY).[2]

Because the combination of trimethoprim and sulfamethoxazole is clearly superior to aerosolized pentamidine in preventing PCP and toxoplasmosis, many practitioners will continue to give it despite mild reactions such as erythroderma, pruritus, and nausea, which often subside with continued treatment. Trimethoprim and sulfamethoxazole are also considerably less expensive than aerosolized pentamidine, which requires specialized equipment. Dapsone may replace aerosolized pentamidine as a second-line treatment, given its systemic effects against PCP and toxoplasmosis, its low cost, and its limited cross-reactivity with trimethoprim and sulfamethoxazole.

TOXOPLASMOSIS

Toxoplasmic encephalitis, like most opportunistic infections in HIV patients, represents an activation of a latent infection. Estimates of the prevalence of previous infection, documented by a positive serologic test for *Toxoplasma*, range from 10% to 96%, with higher rates reported in Western Europe than in the United States. Without prophylaxis, approximately 28% to 33% of patients with positive serologic tests will acquire toxoplasmic encephalitis.[27]

In a retrospective study, 60 patients received trimethoprim 160 mg and sulfamethoxazole 800 mg twice a week, and 95 patients received aerosolized pentamidine. No cases of central nervous system toxoplasmosis occurred in the 22 patients with positive serologic tests in the trimethoprim-and-sulfamethoxazole group, while 12 cases occurred in the 36 patients with positive serologic tests in the aerosolized-pentamidine group.[28] Another trial resulted in seven cases of cerebral toxoplasmosis among 234 patients treated with dapsone 200 mg and pyrimethamine 75 mg weekly and 10 cases among 212 patients treated with aerosolized pentamidine monthly.[29] Clindamycin 300 mg twice a day was compared with pyrimethamine in a clinical trial for prevention of toxoplasmic encephalitis, but the clindamycin arm of the trial was terminated early because of excessive side effects (diarrhea in 31%, rash in 21%).[30]

For patients with fewer than 100 CD4 cells per μL and positive serologic tests for toxoplasmosis who are unable to tolerate trimethoprim and sulfamethoxazole (or possibly dapsone), many practitioners have recommended pyrimethamine alone as primary prophylaxis, but recent trials have shown that pyrimethamine alone is not effective. Other possible regimens include the combination of pyrimethamine and sulfadiazine or sulfadoxine or monotherapy with trimetrexate, clarithromycin, azithromycin, or atovaquone.

FUNGAL INFECTIONS

Few published trials have examined prophylaxis against fungal infections such as candidiasis, cryptococcosis, histoplasmosis, and coccidioidomycosis, although the practice has become widespread because the incidence of these infections is high. Concerns regarding prophylactic treatment of non-life-

threatening infections (eg, oral thrush), include the high cost of many regimens and the potential for organisms to become resistant to these agents. Other infections, such as cryptococcal meningitis, are potentially lethal, while others are major problems in certain regions, such as histoplasmosis in the Midwest and coccidioidomycosis in the American Southwest.

Fluconazole in varying dosages has dramatically reduced the incidence of relapse of oral thrush in several studies. In one small study, nine patients given fluconazole 150 mg weekly had two relapses, compared with five relapses in five patients given placebo.[31] A larger study reported 60 episodes of relapsed thrush among 21 placebo-treated patients, four episodes among 18 patients given fluconazole 50 mg daily, and nine episodes among 19 patients given fluconazole 100 mg daily.[32] Finally, a study with 12 patients given fluconazole 100 mg daily resulted in no cases of oral thrush over the 12 weeks of the study, compared with three cases of thrush among 13 patients given placebo. The authors also noted a decreased incidence of fungal colonization, dermatophytes, onychomycoses, and cryptococcuria in the fluconazole-treated patients, although this is of unclear clinical significance.[33]

In a study comparing 329 patients given fluconazole 100 mg daily with 337 historical controls, both groups had serial blood cultures. There were 16 episodes of cryptococcosis and four episodes of histoplasmosis in the control group vs one episode of cryptococcosis and three episodes of histoplasmosis in the treated group—a 76% reduction in the 1-year incidence of systemic fungal infections. No cases of oral thrush were reported in the fluconazole group.[34]

Various regimens of fluconazole 100 to 200 mg weekly to twice weekly or fluconazole 100 mg daily or every other day have become widespread for fungal prophylaxis in individuals with fewer than 100 CD4 cells per μL. Given the high cost of fluconazole, its relatively long half-life, and its unproved efficacy against any life-threatening infections, a reasonable approach would be to give only 100 mg weekly or twice weekly. A significant concern is the increasing incidence of resistant *Candida* species with the increasing use of fluconazole. Ongoing community trials are assessing the efficacy of fluconazole in dosages of 50 mg three times a week, 200 mg daily, and 400 mg weekly. Itraconazole is also undergoing clinical trials for fungal prophylaxis.

DISSEMINATED *MYCOBACTERIUM AVIUM* COMPLEX INFECTION

Disseminated M *avium* complex (MAC) infections cause fevers, night sweats, weight loss, diarrhea, abdominal pain, hepatosplenomegaly, anemia, and elevated alkaline phosphatase concentrations. Infections typically occur when there are fewer than 50 CD4 cells per μL and usually do not occur with CD4 counts above 100 cells per μL.[1]

The results of two randomized, placebo-controlled, multicenter trials on the prevention of disseminated MAC infection prompted the Food and Drug Administration to approve rifabutin in December 1992. These studies followed, on an intention-to-treat basis, 1146 patients who had fewer than 200 CD4 cells per μL. Of 566 patients taking rifabutin 300 mg daily, 48 acquired disseminated MAC infections, while 102 of 580 patients taking placebo did—a 50% reduction in frequency. Of note, there was no difference in survival between the two groups, but the study was not designed to measure mortality as a primary endpoint.

The US Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium* Complex recommends rifabutin 300 mg daily for patients with fewer than 100 CD4 cells per μL.[35] Side effects of rifabutin include granulocytopenia, thrombocytopenia, rash, gastrointestinal disturbances, and increased metabolism of other medications metabolized in the liver, including zidovudine. The resulting decreased zidovudine serum concentration is of uncertain clinical significance. Other agents with known activity against MAC that are undergoing trials for prophylaxis include the macrolides azithromycin (1200 mg weekly) and clarithromycin (500 mg twice a day both with and without rifabutin). A recent study convincingly demonstrated the lack of utility of clofazimine 50 mg daily in the prophylaxis of disseminated MAC infection in 110 patients with fewer than 100 CD4 cells per μL.[36]

TUBERCULOSIS

The recent rise in the incidence of infections with M *tuberculosis* is largely a result of the HIV epidemic. Most cases of tuberculosis in patients with HIV represent reactivation of a past infection. Chemoprophylaxis appears quite effective, as it is in HIV-negative patients. Difficulty arises in documenting previous exposure to M *tuberculosis* because

cutaneous anergy to purified protein derivative is frequently present in more-advanced HIV infections. One study from New York City found that of 68 anergic HIV-infected patients at high risk for tuberculosis, five acquired active disease.[37]

The Centers for Disease Control and Prevention recommends prophylaxis for tuberculosis in any HIV-infected patient with a tuberculin reaction producing an induration larger than 5 mm.[38] Additionally, previously untreated patients with a documented positive purified protein derivative test, patients with chest roentgenograms suggesting previously untreated tuberculosis, and personal contacts of patients with active tuberculosis should also be considered for prophylaxis.[39] Isoniazid therapy for at least 9 months is recommended. Multidrug-resistant tuberculosis has been reported with increasing frequency among the HIV-infected population.[40–42] No consensus exists regarding chemoprophylaxis for persons exposed to isoniazid-resistant strains, but prophylaxis with agents to which the organism is likely sensitive is probably indicated.

SUMMARY

Prophylaxis against the common opportunistic infections currently represents the single best opportunity to prolong survival for HIV-infected patients. Current recommendations call for prophylaxis against PCP in patients with fewer than 200 CD4 cells per μL and against disseminated MAC infection for patients with fewer than 100 CD4 cells per μL. Data also support prophylaxis against toxoplasmosis and various fungal infections in persons with fewer than 100 CD4 cells per μL. With the incidence of tuberculosis on the rise, all HIV patients at risk for reactivation need prophylaxis. Trials are in progress to assess the ability of oral acyclovir, valacyclovir, and oral ganciclovir to prevent cytomegalovirus disease, a major source of morbidity for patients with advanced HIV infection. Another area for future research is the development of prophylactic agents against cryptosporidiosis and microsporidiosis, two other devastating infections complicating advanced HIV infection.

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