

Opportunistic infections in HIV-infected patients

CHAIRPERSON

STEPHEN D SHAFRAN, MD, FRCPC

THE INITIAL RECOGNITION OF THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) was made by the recognition of opportunistic infections (1,2). Opportunistic infections are the 'AIDS-defining' event in approximately 75% of cases and eventually occur in virtually all AIDS patients. Eight opportunistic infections occur with high frequency in HIV-infected individuals (Table 1).

Of the eight common opportunistic infections, oral and esophageal candidiasis, mucocutaneous herpes simplex infection, and herpes zoster infections are easily managed and while there will be clinical trials of new azole antifungal drugs for candidiasis, and possibly clinical trials of new nucleoside analogues for herpes simplex and varicella-zoster infections, it is unlikely that these newer agents will offer substantial improvements over current therapies. The major unanswered questions in HIV-associated opportunistic infections relate to the other five opportunistic infections which will be discussed in turn.

PNEUMOCYSTIS CARINII PNEUMONIA

Pneumocystis carinii pneumonia (PCP) is the AIDS-defining condition in about 65% of cases and ultimately occurs in about 85% (3). Because of the current recommendations for both primary and secondary prophylaxis (4), it is anticipated that the incidence of PCP will diminish substantially in the future.

PCP treatment - Answered questions: Two studies have compared the relative efficacy of trimethoprim-sulphamethoxazole (TMP-SMZ) with that of intravenous pentamidine (5,6). The earlier study of 40 patients found a higher survival rate in pentamidine-treated patients (95 versus 75%), but this did not quite achieve significance ($P=0.09$) (5). The results of this trial are difficult to interpret as approximately half of the patients

TABLE 1
Common opportunistic infections in HIV-infected individuals

Opportunistic infection	AIDS-defining event (%)	Ultimate prevalence (%)
<i>Pneumocystis carinii</i> pneumonia	65	85
Oral and esophageal candidiasis	6	?80
Mucocutaneous herpes simplex infection	2	60
Herpes zoster	N/A	?
<i>Mycobacterium avium</i> complex infection	1-2	50
Cytomegalovirus disease	2	10
Cerebral toxoplasmosis	3	10
Cryptococcosis	2	5-13

were crossed over from their initial assigned therapy due to drug toxicity.

In the second study of 70 patients, the survival in TMP-SMZ-treated patients was higher (86 versus 61%) and this difference was statistically significant ($P=0.03$) (6). Furthermore, there were no cross-overs during this study. It appears, therefore, that TMP-SMZ may be more effective than pentamidine in subjects able to remain on therapy.

Medina et al (7) conducted a prospective randomized trial comparing TMP-SMZ with a combination of TMP and dapsone in AIDS-associated PCP. They found equivalent efficacy of the two therapies but lesser toxicity in the TMP and Dapsone group, of which 30% experienced treatment limiting adverse effects, compared with 57% of patients treated with TMP-SMZ ($P<0.025$).

Two studies have compared the relative efficacy of intravenous pentamidine with that of aerosolized pentamidine (8,9). Both studies demonstrated clearly that aerosolized pentamidine was less effective than intravenous pentamidine.

The role of adjunctive corticosteroids has also been studied in AIDS-associated PCP. Of five randomized con-

Workshop participants: W Cameron, I Chiu, G Evans, I Fong, G Garber, C Hankins, J Mendelson, R Morisset, P Phillips, I Salit, F Smail, G Taylor, H Vellend

Correspondence: Dr Stephen Shafran, Division of Infectious Diseases, Department of Medicine, 2E4.11 Walter Mackenzie Health Sciences Centre, University of Alberta, Edmonton, Alberta T6G 2B7

trolled trials, three found a survival advantage for steroids including the two largest studies (10). A fourth study found improved oxygenation and long term exercise tolerance in the steroid-treated group (11). Only one of the five studies found no benefit from corticosteroids (12). An expert panel has recently issued a consensus statement recommending the use of adjunctive corticosteroids in AIDS-associated PCP when the initial room air PO_2 is below 70 mmHg (10).

Unanswered questions: The major unanswered questions in PCP treatment relate to the relative efficacy of therapies other than TMP-SMZ, TMP-dapsone and pentamidine. Specifically, the relative efficacy of clindamycin plus primaquine (13), trimetrexate (14), eflornithine (alpha-DFMO) (15), and newer agents such as piritrexim (16), 9-deazainosine (17) and 566C80 (18).

A trial comparing clindamycin and primaquine to TMP-SMZ has been proposed by Dr Emil Toma through the Canadian HIV Clinical Trials Network and it is hopeful that this trial will get underway in the near future. Trials with trimetrexate and 566C80 are currently ongoing in the United States through the AIDS Clinical Trial Group (ACTG).

PCP prophylaxis – Answered questions: The efficacy of TMP-SMZ in the primary prophylaxis of PCP in HIV-infected individuals has been examined in a placebo-controlled trial in patients with Kaposi's sarcoma (19). This study showed a potent effect of TMP-SMZ. The dose used was relatively high (one double strength tablet bid) and was associated with significant toxicity. A recent uncontrolled study using one double strength tablet three days a week was 100% effective (20) indicating that lower doses of TMP-SMZ are also effective for PCP prophylaxis.

Aerosolized pentamidine has also been shown to be effective in PCP prophylaxis in a placebo-controlled trial (unpublished data) when given by ultrasonic nebulizer. Aerosolized pentamidine given by jet nebulizer is also effective, as demonstrated in a comparison of three different doses where the two higher dosing regimens were clearly superior to the lowest dose used, which has been considered by some to be a pseudoplacebo (21).

Controlled trials of other potential drugs for PCP prophylaxis have not been published, but uncontrolled favorable results have been reported using dapsone alone (22), fansidar (23) and clindamycin plus primaquine (24).

Unanswered questions: There is, as yet, no published study comparing the relative efficacy of the two most commonly used prophylactic treatments, namely TMP-SMZ and aerosolized pentamidine. However, such a trial, in secondary prophylaxis only, has been completed by the ACTG (protocol 021). There also has been no comparison of the two major devices for nebulizing aerosolized pentamidine, namely the Fisoneb ultrasonic nebulizer and the Respigard II jet nebulizer (several other nebulizers exist). Furthermore, the optimal neb-

ulizer, dose and body positioning for delivery of aerosolized pentamidine remain to be established (25).

MYCOBACTERIUM AVIUM COMPLEX INFECTION

Mycobacterium avium complex (MAC) infection is the AIDS-defining event in fewer than 5% of cases (Federal Centre for AIDS data). However, MAC infection is diagnosed during life in 15 to 30% of AIDS patients and is found at autopsy in up to 53% of cases (26-28). While MAC infection is clearly a common late complication in AIDS, its contribution to mortality is questionable (29). Nevertheless, MAC infection can be an important cause of morbidity, causing fever, weight loss, diarrhea and, less frequently, focal disease in the biliary tract, lung and central nervous system (28). MAC isolates are characteristically resistant in vitro to most antimycobacterial agents (26,28), recognizing that there are no clearly accepted standards for susceptibility testing for nontuberculous mycobacteria.

Answered questions: There are essentially no answered questions in this area.

Unanswered questions: There is considerable debate as to the merits of therapy for MAC infection due to the following factors.

- The contribution of MAC to AIDS mortality is minimal.
- MAC isolates are multiresistant in vitro.
- In a number of patients, MAC infection is diagnosed at such an advanced stage of AIDS that treatment may be inappropriate.
- The addition of three or four drugs to patients who generally are already taking antiretroviral, anti-PCP and anticandidal therapy is problematic.
- The results of many of the early reports of treatment have been unfavorable.

No controlled clinical trials in the treatment of MAC infection have ever been published, although a pilot study of clarithromycin monotherapy has been reported in abstract form (30). The initial reports of the results of treating MAC infection in AIDS patients were unfavorable (31-33); however, three more recent reports of combination drug therapy have been very encouraging (34-36). For this reason, the pendulum appears to be swinging towards treating most symptomatic patients.

In January 1991, the Canadian HIV Trials Network approved a multicentre trial comparing two different regimens of combination therapy for MAC bacteremia. It was anticipated that the trial would start in the summer of 1991.

In the United States, a trial is proposed to compare the combination of rifabutin, ethambutol and clofazimine to ethambutol and clofazimine without rifabutin. Furthermore, it is anticipated that trials using clarithromycin will commence within the next year, based on the encouraging pilot study from France noted above (30).

Finally, there is presently an ongoing multicentre

United States/Canada double-blinded trial evaluating the efficacy of rifabutin monotherapy in the prevention of MAC infection in AIDS patients with CD4 lymphocyte counts below $200 \times 10^6/L$, who have no previous history of mycobacterial infection.

CYTOMEGALOVIRUS INFECTION

Nearly all HIV infected patients are cytomegalovirus (CMV) seropositive (37). Furthermore, isolation of CMV from a variety of body sites in the absence of clear disease occurs commonly, particularly in association with marked CD4 lymphopenia. Although CMV has been isolated from nearly every organ in AIDS patients, definite evidence of disease occurs most commonly in the retina and bowel (37,38). CMV retinitis occurs in 5 to 10% of AIDS patients and CMV enteritis is about half as prevalent (37,38). It is unusual for both retinitis and enteritis to occur in the same individual (37,38).

Answered questions: In the case of retinitis, intravenous ganciclovir has been approved for use in both the United States and Canada on the basis of open trials demonstrating efficacy (39). Placebo-controlled trials have not been conducted because of an impression that disease invariably progresses in the absence of therapy. While approximately 85% of patients with CMV retinitis have a favorable response to ganciclovir, it is clear, that the majority of individuals will relapse after ganciclovir therapy necessitating maintenance therapy (37,38,40); however, even with maintenance therapy, deterioration occurs in at least 50% of patients (38,40). Foscarnet has also been shown to be effective for CMV retinitis in uncontrolled trials (41,42).

Unanswered questions: The obvious unanswered question is the comparison of the relative efficacy and toxicity of ganciclovir and foscarnet. Such a study is underway in the United States. The same trial was approved by the Canadian HIV Trials Network, but insufficient funding was available. A similar study in only 40 patients was conducted in England and found similar response rates to the two drugs (43).

The addition of immunoglobulin (either polyclonal or CMV hyperimmune) to ganciclovir has improved the response of CMV pneumonia in bone marrow transplant recipients (44,45). The role of additional immunoglobulin therapy in CMV retinitis is unclear, but a pilot study suggested a lack of efficacy (46).

Intravitreal ganciclovir therapy has been successful (47,48), but generally has been reserved for patients who experienced excessive myelotoxicity with systemic ganciclovir. The relative efficacy of the intravitreal versus the intravenous route has not been compared.

There are presently no published controlled trials of effective therapy for HIV-associated CMV enteritis, although there are anecdotal reports of favorable responses with ganciclovir (37,38). In bone marrow transplant recipients, ganciclovir was no more effective than placebo in relieving symptoms of proven CMV enteritis,

despite a definite antiviral effect (49). A placebo-controlled trial of ganciclovir for CMV colitis in 62 AIDS patients has been presented in abstract form (50). There was a marked antiviral effect and a modest but not statistically significant clinical benefit favouring ganciclovir.

CEREBRAL TOXOPLASMOSIS

Cerebral toxoplasmosis occurs in approximately 10% of AIDS patients (51). Nearly all cases occur in patients seropositive for *Toxoplasma gondii* of whom approximately 30% will develop toxoplasmosis (51,52).

Answered questions: It is clear that most AIDS patients with cerebral toxoplasmosis respond favorably to pyrimethamine and sulphadiazine therapy (51-55). However, most patients successfully treated will relapse if therapy is stopped altogether (53-55); therefore, maintenance therapy with reduced dose pyrimethamine and sulphadiazine is the standard treatment (51,53,56).

Clindamycin with or without pyrimethamine is also effective in the treatment of cerebral toxoplasmosis (57-59). The relative efficacy of sulphadiazine plus pyrimethamine versus clindamycin plus pyrimethamine for cerebral toxoplasmosis was evaluated by the California Collaborative Treatment Group (60). The two regimens did not appear to differ in efficacy, although the sample size precludes a definitive statement of equivalence.

Unanswered questions: A major unanswered question relates to the role of prophylaxis in toxoplasma seropositive patients. It has been argued that prophylaxis is likely to be effective (61), and should be evaluated (61, 62). At this point, such a trial has not been published.

A potential problem for any study in cerebral toxoplasmosis will be whether brain biopsy is required for diagnosis, since many clinicians do not routinely recommend confirming the diagnosis by brain biopsy (63). This issue must be clearly addressed in any such trial.

CRYPTOCOCCOSIS

Cryptococcosis is reported in 5 to 13% of AIDS cases (64), with a lower incidence likely if oral azole therapy is initiated early to treat mucosal candidiasis.

Therapy – Answered questions: Two major trials have compared the efficacy of amphotericin B with that of fluconazole (65,66). Larsen et al (65) compared the combination of amphotericin B at a dosage of 0.7 mg/kg/day, and flucytosine 150 mg/kg/day with fluconazole 400 mg/day and found that six of six amphotericin-treated patients had sterile cerebrospinal fluid at week 10, compared with five of 14 treated with fluconazole, a difference which was highly significant. As well, sterilization of the cerebrospinal fluid occurred significantly more rapidly with amphotericin B.

In contrast, the presently unpublished study conducted jointly by the Mycosis Study Group of the National Institute of Allergic and Infectious Diseases and the ACTG showed comparable efficacy of the two treatments.

Secondary prophylaxis: Fluconazole at a dose of 200 mg/day reportedly is more effective than either placebo or amphotericin B given intravenously at a dosage of 1 mg/kg once a week in the secondary prophylaxis of cryptococcal infection in AIDS patients (67,68).

Treatment – Unanswered questions: The relative efficacy of amphotericin B versus triazoles is not entirely resolved, particularly as higher doses of triazoles than those used in previous trials may be tolerated. Furthermore, even if amphotericin B is the initial agent used, it may be possible to switch to triazoles at an earlier point than 10 weeks, perhaps dictated by a specified period after initial sterilization.

Flucytosine's role in the treatment of cryptococcosis remains controversial. In a frequently cited study conducted in the pre-AIDS era, the combination of amphotericin B plus flucytosine was more effective than amphotericin B alone (69). This study has been criticized, however, because of the low dosage of amphotericin B chosen in both arms, and because the efficacy of the amphotericin B monotherapy arm was lower than historic controls (70). A similar trial has not been conducted in AIDS patients. However, uncontrolled data from San Francisco do not suggest that combination therapy is more effective than amphotericin B monotherapy (71). Also, the myelosuppressive properties of flucytosine make it difficult to use in AIDS patients.

The role of liposome-encapsulated amphotericin B in human cryptococcosis has not been evaluated, but such therapy is effective in murine cryptococcosis (72).

Prophylaxis: Whereas triazole antifungals such as itraconazole and saperconazole may prove to be as effective as fluconazole for secondary prophylaxis of cryptococcosis, is extremely doubtful that they will prove to be more effective.

PROPOSED CLINICAL TRIALS

On the basis of the above review, and extensive discussions in the workshop, the working group proposed two clinical trials.

ADDENDUM: Dr Shafran wishes to stress that AIDS is a rapidly changing field and that the manuscript was written in April 1991; thus, significant changes have occurred in this area since that time.

REFERENCES

- 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.
- 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.
- Murray JF, Mills J. Pulmonary infectious complications of human immunodeficiency virus infection. Part II. *Am Rev Respir Dis* 1990;141:1582-98.

Trial 1: 'A prospective randomized comparative trial of TMP plus dapsone versus aerosolized pentamidine for the prevention of PCP and toxoplasmosis.' The purpose of this trial is to answer two questions. First, to determine the relative efficacy of aerosolized pentamidine versus an orally absorbed systemic therapy for PCP prevention. TMP plus dapsone was chosen over TMP-SMZ because TMP plus dapsone was shown to be better tolerated in a PCP treatment study (7), and it was felt that it was less likely that such a trial was taking place elsewhere.

The second is to determine whether there is a role for prophylactic therapy for toxoplasmosis in HIV-infected individuals who are toxoplasma-seropositive. Although pyrimethamine plus sulphadiazine is the best studied treatment for toxoplasmosis, TMP plus dapsone was selected for the following reasons: this selection would facilitate answering two important clinical questions with one study design; and this combination is known to be effective in vitro and in animal models of toxoplasmosis (73,74).

Therefore, in order to conduct this study properly, it was acknowledged that toxoplasma serology would be done in a single reference laboratory and that patients would be stratified according to their toxoplasma serological status. Patients were then to be randomly allocated 1:1 to aerosolized pentamidine versus TMP plus dapsone.

Trial 2: The working group felt frustrated by the clinical problem of CMV enteritis. Clinicians reported a perceived pressure to administer ganciclovir therapy in order to feel that something is being done, despite a lack of efficacy data. A consensus regarding the study design was not finalized. It was acknowledged that a placebo-controlled trial is indeed ethical, but might be impossible to carry out. Alternative trials included a comparison of ganciclovir with foscarnet, or a comparison of ganciclovir alone with ganciclovir plus either CMV immune globulin or polyclonal intravenous immunoglobulin.

- Masur H, Allegra C, Armstrong D, et al. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. *MMWR* 1989;38:1-9.
- Wharton JM, Coleman DL, Wofsy CB, et al. Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1986;105:37-44.
- Settler FR, Cowan R, Nielsen DM, Ruskin J. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: A prospective, noncrossover study. *Ann Intern Med* 1988;109:280-7.
- Medina I, Mills J, Leoung C, et al. Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A controlled trial of

- trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med* 1990;323:776-82.
8. Soo Hoo GW, Mohsenifar Z, Meyer RD. Inhaled or intravenous pentamidine therapy for *Pneumocystis carinii* pneumonia in AIDS: A randomized trial. *Ann Intern Med* 1990;113:195-202.
 9. Conte JE, Chernoff D, Feigal DW, Joseph P, McDonald C, Golden JA. Intravenous or inhaled pentamidine for treating *Pneumocystis carinii* pneumonia in AIDS: A randomized trial. *Ann Intern Med* 1990;113:203-9.
 10. Masur H, Meier P, McCutchan JA, et al. Special report: Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med* 1990;323:1500-5.
 11. Montaner JSG, Lawson LM, Levitt N, Belzberg A, Schechter MT, Ruedy J. Corticosteroids prevent early deterioration in patients with moderately severe *Pneumocystis carinii* pneumonia and the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1990;113:14-20.
 12. Clement M, Edison R, Turner J, et al. Corticosteroids as adjunctive therapy in severe *Pneumocystis carinii* pneumonia: A prospective placebo-controlled trial. *Am Rev Respir Dis* 1989;139:A250. (Abst)
 13. Toma E, Poisson M, Phaneuf D, Fournier S, Morisset R, Vega C. Clindamycin with primaquine for *Pneumocystis carinii* pneumonia. *Lancet* 1989;i:1046-8.
 14. Allegra CJ, Chabner BA, Tuazon CU, et al. Trimetrexate for the treatment of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1987;317:978-85.
 15. Golden JA, Sjoerdsma A, Santi DV. *Pneumocystis carinii* pneumonia treated with alpha-difluoromethylornithine. A prospective study among patients with the acquired immunodeficiency syndrome. *West J Med* 1984;141:613-23.
 16. Queener SF, Bartlett MS, Jay MA, Durkin MM, Smith JW. Activity of lipid-soluble inhibitors of dihydrofolate reductase against *Pneumocystis carinii* in culture and in a rat model of infection. *Antimicrob Agents Chemother* 1987;31:1323-7.
 17. Smith JW, Bartlett MS, Queener MM, et al. *Pneumocystis carinii* pneumonia therapy with 9-deazainosine in rats. *Diagn Microbiol Infect Dis* 1987;7:113-8.
 18. Hughes WT, Kennedy W, Shenep J, et al. Safety and pharmacokinetics of 566C80, a hydroxynaphthoquinone with anti-*Pneumocystis carinii* activity: A phase I study in human immunodeficiency virus (HIV)-infected men. *J Infect Dis* 1991;163:843-8.
 19. Fischl MA, Dickinson GM, LaVoie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. *JAMA* 1988;259:1185-9.
 20. Ruskin J, LaRiviere M. Low-dose co-trimoxazole for prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus disease. *Lancet* 1991;337:468-71.
 21. Leoung GS, Feigal DW, Montgomery AB, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia. *N Engl J Med* 1990;323:769-75.
 22. Lucas CR, Sandland AM, Mijch A, Simpson JM. Primary dapsone chemoprophylaxis for *Pneumocystis carinii* pneumonia in immunocompromised patients infected with the human immunodeficiency virus. *Med J Aust* 1989;151:30-3.
 23. Gottlieb MS, Knight S, Mitsuyasu R, Weisman J, Roth M, Young LS. Prophylaxis of *Pneumocystis carinii* infections in AIDS with pyrimethamine-sulfadoxine. *Lancet* 1984;ii:398-9.
 24. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with AIDS. *South Med J* 1990;83:403-4.
 25. Baskin MI, Abd AG, Ilowite JS. Regional deposition of aerosolized pentamidine: Effects of body position and breathing pattern. *Ann Intern Med* 1990;113:677-83.
 26. Hawkins CC, Gold JWM, Whimbey E, et al. *Mycobacterium avium* complex infections in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1986;105:184-8.
 27. Dawson DJ. Infection with *Mycobacterium avium* complex in Australian patients with AIDS. *Med J Aust* 1990;153:466-8.
 28. Jacobson MA. Mycobacterial diseases: Tuberculosis and *Mycobacterium avium* complex. *Infect Dis Clin North Am* 1988;2:465-74.
 29. Chaisson RE, Hopewell PC. Mycobacteria and AIDS mortality. *Am Rev Respir Dis* 1989;139:1-3. (Edit)
 30. Dautzenberg B, Legris S, Truffot C, et al. Double blind study of efficacy of clarithromycin versus placebo in *Mycobacterium avium-intracellulare* infection in AIDS patients. *Am Rev Respir Dis* 1990;141:A615. (Abst)
 31. Greene JB, Sidhu GS, Lewin S, et al. *Mycobacterium avium-intracellulare*: A cause of disseminated life threatening infection in homosexuals and drug abusers. *Ann Intern Med* 1982;97:539-46.
 32. Hawkins CC, Gold TWM, Whimbey E, et al. *Mycobacterium avium* complex infections in patients with acquired immunodeficiency syndrome. *Ann Intern Med* 1986;105:184-8.
 33. Masur H, Tuazon C, Gill V, et al. Effect of combined clofazimine and ansamycin therapy on *Mycobacterium avium-Mycobacterium intracellulare* bacteremia in patients with AIDS. *J Infect Dis* 1987;155:127-9.
 34. Agins BD, Berman DS, Spicehandler D, El-Sadr W, Simberkoff MS, Rahal JJ. Effects of combined therapy with ansamycin, clofazimine, ethambutol, and isoniazid for *Mycobacterium avium* infection in patients with AIDS. *Infect Dis* 1989;159:784-7.
 35. Hoy J, Mijch A, Sandland M, Grayson L, Lucas R, Dwyer B. Quadruple-drug therapy of *Mycobacterium avium-intracellulare* bacteremia in AIDS patients. *J Infect Dis* 1990;161:801-5.
 36. Chiu J, Nussbaum J, Bozette S, et al. Treatment of disseminated *Mycobacterium avium* complex infection in AIDS with amikacin, ethambutol, rifampin, and ciprofloxacin. *Ann Intern Med* 1990;113:358-61.
 37. Jacobson MA, Mills J. Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988;108:585-94.
 38. Jacobson MA, O'Donnell JJ, Porteous D, Brodie HR, Feigal D, Mills J. Retinal and gastrointestinal disease due to cytomegalovirus in patients with the acquired immune deficiency syndrome: Prevalence, natural history, and response to ganciclovir therapy. *Q J Med* 1988;254:473-86.
 39. Holland GN, Buhles WC Jr, Mastre B, Kaplan HJ, the UCLA CMV Retinopathy Study Group. A controlled retrospective study of ganciclovir treatment for cytomegalovirus retinopathy. *Arch Ophthalmol* 1989;107:1759-66.
 40. Bloom JN, Palestine AG. The diagnosis of cytomegalovirus retinitis. *Ann Intern Med* 1988;109:963-9.
 41. Walmsley SL, Chew E, Read SE, et al. Treatment of

- cytomegalovirus retinitis with trisodium phosphonoformate hexahydrate (foscarnet). *J Infect Dis* 1988;157:569-72.
42. Jacobson MA, O'Donnell JJ, Mills J. Foscarnet treatment of cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome. *Antimicrob Agents Chemother* 1989;33:736-41.
 43. Graeme M, Mathalone B, Gazzard B. An open randomized comparative study of foscarnet and ganciclovir in the treatment of CMV retinitis. Presented at the VIth International Conference on AIDS, 1990. (Abst)
 44. Emanuel D, Cunningham I, Jules-Elysee K, et al. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988;109:777-82.
 45. Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. *Ann Intern Med* 1988;109:783-8.
 46. Jacobson MA, O'Donnell JJ, Rousell R, Dionian B, Mills J. Failure of adjunctive cytomegalovirus intravenous immune globulin to improve efficacy of ganciclovir in patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis: A phase 1 study. *Antimicrob Agents Chemother* 1990;34:176-8.
 47. Ussery FM III, Gibson SR, Conklin RH, Plot DF, Stool EW, Conklin AJ. Intravitreal ganciclovir in the treatment of AIDS-associated cytomegalovirus retinitis. *Ophthalmol* 1988;95:640-8.
 48. Heinemann MH. Long-term intravitreal ganciclovir therapy for cytomegalovirus retinopathy. *Arch Ophthalmol* 1989;107:1767-72.
 49. Reed EC, Wolford JL, Kopecky KJ, et al. Ganciclovir for the treatment of cytomegalovirus gastroenteritis in bone marrow transplant patients. A randomized, placebo-controlled trial. *Ann Intern Med* 1990;112:505-10.
 50. Dietrich D, Kotler D, Busch D, et al. Randomized, placebo-controlled study of ganciclovir treatment of cytomegalovirus (CMV) colitis in AIDS patients. Presented at the VIth International Conference on AIDS, 1990. (Abst)
 51. Israelski DM, Remington JS. Toxoplasmic encephalitis in patients with AIDS. *Infect Dis Clin North Am* 1988;2:429-45.
 52. Luft BJ, Brooks RC, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA* 1984;252:913-7.
 53. Navia BA, Petito CK, Gold JWM, Cho, ES, Jordan BD, Price RW. Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome: Clinical and neuropathological findings in 27 patients. *Ann Neurol* 1986;9:224-38.
 54. Wanke C, Tuazon CU, Kovacs A, et al. Toxoplasma encephalitis in patients with acquired immune deficiency syndrome: Diagnosis and response to therapy. *Am J Trop Med Hyg* 1987;36:509-16.
 55. Haverkos HW, The TE Study Group. Assessment of therapy for toxoplasma encephalitis. *Am J Med* 1987;82:907-14.
 56. Lepout C, Raffi F, Matheron SS, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. *Am J Med* 1988;84:94-100.
 57. Hofflin JM, Remington JS. Clindamycin in a murine model of toxoplasmic encephalitis. *Antimicrob Agents Chemother* 1987;31:492-6.
 58. Rolston KVI, Hoy J. Role of clindamycin in the treatment of central nervous system toxoplasmosis. *Am J Med* 1987;83:551-4.
 59. Dannemann BR, Israelski DM, Remington JS. Treatment of toxoplasmic encephalitis with intravenous clindamycin. *Arch Intern Med* 1988;148:2477-82.
 60. Dannemann BR, McCutchan JA, Israelski DM, et al. Treatment of toxoplasmic encephalitis in patients with AIDS: A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfonamides. Presented at the 30th ICAAC, 1990. (Abst)
 61. Rose DN. Prevention of toxoplasma activation among immunocompromised patients: A decision analysis. Presented at the VIth International Conference on AIDS, 1990. (Abst)
 62. Girard PM, Pocardalo JJ, Murray JF. Primary prophylaxis against common infectious diseases in persons with human immunodeficiency virus infection. *Am Rev Respir Dis* 1991;143:447-50.
 63. Cohn JA, McMeeking A, Cohen W, Jacobs J, Holzman RS. Evaluation of the policy of empiric treatment of suspected toxoplasma encephalitis in patients with the acquired immunodeficiency syndrome. *Am J Med* 1989;86:521-7.
 64. Dismukes WE. Cryptococcal meningitis in patients with AIDS. *J Infect Dis* 1988;157:624-8.
 65. Larsen RA, Leal MAE, Chan LS. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS: A randomized trial. *Ann Intern Med* 1990;113:183-7.
 66. Data on file, Pfizer Central Research, Groton, Connecticut.
 67. Bozzette SA, Larsen RA, Chill 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.
 68. Powderly W, Cloud MSG, Dismukes W, et al. Fluconazole versus amphotericin B as maintenance therapy for prevention of relapse of AIDS-associated cryptococcal meningitis. Presented at the 30th ICAAC, 1990. (Abst)
 69. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med* 1979;301:126-31.
 70. Sabetta JR, Andriole V. Cryptococcal infection of the central nervous system. *Med Clin North Am* 1985;69:333-44.
 71. Chuck SL, Sande MA. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. *N Engl J Med* 1989;321:794-9.
 72. Graybill JR, Craven PC, Taylor RL, Williams DM, Magee WE. Treatment of murine cryptococcosis with liposome-associated amphotericin B. *J Infect Dis* 1982;145:748-52.
 73. Allegra CJ, Boorman D, Kovacs JA, et al. Interaction of sulfonamide and sulfone compounds with *Toxoplasma gondii* dihydropteroate synthase. *J Clin Invest* 1990;85:371-9.
 74. Derouin F, Piketty C, Chastang C, Chau F, Rouveix B, Pocardalo JJ. Antitoxoplasma effects of dapsone alone and combined with pyrimethamine. *Antimicrob Agents Chemother* 1991;35:252-5.



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

